

PHARMACOLOGY
MATERIA MEDICA AND
THERAPEUTICS



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PHARMACOLOGY MATERIA MEDICA AND THERAPEUTICS

(R. Ghosh's *Materia Medica and Therapeutics*)

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PREFACE TO THE FIFTEENTH EDITION

SINCE the publication of the last edition in 1936 the Addendum to the British Pharmacopœia was published. Advantage has therefore been taken in the present edition not only to incorporate all the remedies which have been officially recognised in the Addendum but to once again thoroughly revise the entire text. While minor alterations have been made almost in every page, certain monographs have been rewritten, and a few modified, to incorporate all the recent pharmacological works.

Of the important advances made within recent years may be mentioned the use of mandelic acid and its salts in the treatment of urinary infections; sulphanilamide and its derivatives in streptococcal and other infections; protamine-zinc-insulin in diabetes mellitus; and nicotinic acid in pellagra; all of which have been for the first time discussed. Other additions which require special mention are the use of congo red as a coagulant; snake venoms in the treatment of hæmorrhage and nerve pain; heparin as an anticoagulant; glycine and prostigmine in myasthenia gravis; benzedrine as a sympathetic stimulant; histidine in peptic ulcer; vinyl ether and cyclopropane as general anæsthetics; and magnesium trisilicate as an adsorbent.

In the last edition a few graphs were first introduced not only to illustrate the action of drugs but also to enable the student to take an intelligent interest in the study of the subject. A few more have been added in the present edition and some of the old ones have been replaced by better and more explanatory ones.

The importance of the knowledge of organic chemistry and the advances made in the different synthetic drugs are stressed by giving the constitutional formulæ of different drugs and compounds.

To avoid misinterpretations and for the convenience of the prescriber and dispenser, the abbreviations of the Latin names of drugs, as given in the British Pharmacopœia, have been given, and it is expected that these should be followed.

Attention was drawn in the last edition to the defective system of teaching pharmacology as a pure science divorced from therapeutics. Every attempt has therefore been made to treat pharmacology as an applied subject so as to arouse the interest of the student in scientific therapeutics. It should however be emphasised that the subject can only be taught properly when the knowledge gained in the class room is supplemented by its practical application at the bedside.

I trust that these changes will enhance the usefulness of the book and that it will continue to maintain its position as a standard work for students and a reliable guide for practitioners.

DEPARTMENT OF PHARMACOLOGY
CARMICHAEL MEDICAL COLLEGE

B. N. GHOSH

THE FIRST EDITION OF THIS VOLUME WAS
DEDICATED TO THE
PRINCIPAL OF THE CALCUTTA MEDICAL
COLLEGE

IN GRATEFUL REMEMBRANCE OF THE
EDUCATION RECEIVED THEREIN
BY THE AUTHOR

CONTENTS

PART I MATERIA MEDICA PROPER

	PAGE
Definitions	1
Drugs	3
Composition of Drugs	3-7
Impurities of Drugs	7
British Pharmacopœia and Pharmaceutical Processes	7-9
Weights and Measures	9-11
Standardisation of Drugs and Biological Assay	11-14
Pharmacopœial Preparations	14-36
Non-official Preparations	36-42

PART II. ADMINISTRATION OF DRUGS

Channels for Administration of Drugs	43-47
Factors modifying the action of Drugs	47-51
Antagonism and Synergism	51-52
Incompatibility	52-54
Explosive Combinations	54-55
Poisonous Combinations	55
Combination of Drugs	55
Weights and Measures in a Prescription	55-56
Prescription Writing	57-59
Elegant Prescriptions	59
Directions to the Patient	59-60
Prescriptions for Children	60

PART III. PHARMACOLOGY AND THERAPEUTICS

How Drugs Act	61-66
GROUP	
I The Alkalies and Metals of Alkaline Earth Potassium, Sodium, Ammonium, Lithium, Calcium, Magnesium, Barium	66-108
II Acids Acetic, Trichloroacetic, Citric, Tartaric, Hydrochloric, Nitric, Phosphoric, Hypophosphorous, Sulphuric, Lactic	108-115
III Heavy Metals Lead, Silver, Zinc, Copper, Alum, Kaolin, Gold, Thallium	116-136
IV Metalloids Chromium, Phosphorus	136-138
V Drugs Acting on the Nervous System	139-140
Class A Drugs acting on the Brain	140-141
1. Intoxicant: Alcohol	141-151

GROUP	PAGE
2. General Anæsthetics and Narcotics : Chloroform, Ether, Vinyl Ether, Ethylene, Cyclopropane, Nitrous Oxide, Ethyl Chloride	151-169
3. Hypnotics	169-172
1. Alkaloidal Hypnotics : Opium, Morphine, Codeine, Diamorphine, Cannabis Indica	172-191
2 Aliphatic Hypnotics	
(a) Chloral Group : Chloral Hydrate, Butylchloral Hydrate, Chloral Formamide, Chlorbutol	191-196
(b) Aldehyde Alcohol Group : Paraldehyde, Avertin, Amylene Hydrate	196-198
(c) Sulphonal Group : Sulphonal, Methylsulphonal, Ethylsulphonal	198-200
(d) Urea Derivatives : Barbitone, Soluble Barbitone, Carbomal, Phenobarbitone, Soluble Phenobarbitone, Nembutal, Amytal, Evipan, Urethane	200-208
3. Inorganic Hypnotics : Bromides	208-213
Class B. Drugs Acting on the Cord : Nux Vomica and Strychnine	213-220
Class C. Drugs Acting on the Sympathetic and Parasympathetic Systems	220-223
Drugs Acting on the Eye	223-225
1. Drugs Stimulating the Parasympathetic endings : Muscarine, Pilocarpine, Physostigmine, Choline	225-234
2. Drugs Depressing the Parasympathetic endings : Belladonna, Hyoscyamus, Stramonium	234-249
Class D. Drugs Acting on the Motor Nerve endings and Ganglia : Curara, Nicotine, Conium, Gelsemium, Sparteine	249-251
Class E. Drugs Depressing the Sensory Nerve endings : Cocaine, Amylocaine, Benzocaine, Orthocaine, Procaine, Percaine	251-262
VI Drugs Acting on the Cardio-vascular System	263
Class A. Drugs Acting on the Heart	263-266
1. Cardiac Tonics : Digitalis, Strophanthus, Squill, Apocynum	266-281
2. Cardiac Depressants : Aconite	281-284
Class B. Drugs Acting on the Vessels	284-287
1. Drugs Raising the Blood-pressure (Vasoconstrictors) : Adrenaline, Ephedrine, Benzedrine	287-297
2. Drugs Lowering the Blood-pressure (Vaso-dilators) : Amyl Nitrite, Nitroglycerin, Erythrol Tetranitrate, Sodium Nitrite	297-302
VII Drugs Acting on the Respiratory System	302-304
Class A. Carbon Dioxide, Oxygen	304-308

CONTENTS

xi

GROUP		PAGE
	Class B. Expectorants ...	308-309
	Ipecacuanha, Apomorphine Hydrochloride, Senega, Quillaja ...	309-318
	Class C. Bronchial Antispasmodics: Lobelia, Giindelia	318-320
	Class D. Bronchial Sedatives: Prunus Serotina	320-321
	Class E. Pulmonary Antiseptics: Guaiacol, Creosote	321-323
	Class F. Drugs used for X-Ray examination of Lungs and Bronchioles: Iodised oil	323-324
VIII	Drugs Acting on the Gastro-intestinal Tract	
	Salivary Secretion	324-325
	Drugs Acting on the Stomach	325-328
	Class A. Vegetable Bitters: Calumba, Quassia, Gentian, Chnata, Serpentry, Bitter-orange Peel	328-331
	Class B. Digestive Ferments: Pepsin, Pancreatin, Papain, Malt, Taka Diastase	331-335
	Class C. Emetics	335-336
	Class D. Antiemetics: Acid Hydrocyanic Dilute	336-338
	Class E. Adsorbents: Charcoal	339
	Drugs Acting on the Intestine	339-341
IX	Purgatives	341-343
	1. Saline Purgatives: Acid Potassium Tartrate, Sodium Potassium Tartrate, Sodium Sulphate, Sodium Phosphate, Acid Sodium Phosphate, Magnesium Sulphate	343-348
	2. Laxatives: Agar, Tamarind, Cassia, Manna, Castor Oil	348-350
	3. Anthracene Purgatives: Aloe, Rhubarb, Senna, Cascara Sagrada, Phenolphthalein	350-358
	4. Drastic Purgatives: Ipomœa, Scammony Resin, Jalap, Croton Oil, Colocynth	358-361
	5. Cholagogue Purgatives: Podophyllum, Iridin, Euonymus Bark	361-363
X	Drugs Acting on the Liver	363-365
	Class A. Cholagogues: Extract of Ox Bile	365
	Class B. Drugs used for Diagnostic Purposes Iodophthalein	365-366
XI	Astringents: Tannic Acid, Catechu, Rhatany, Hamamelis	367-372
XII	Anthelmintics	372-373
	Santonin, Filix Mas, Pelletierine Tannate, Carbon Tetrachloride, Oil of Chenopodium	373-379
XIII	Drugs Acting on the Kidneys	379-382
	Class A. Diuretics: Water, Caffeine, Theobromine and Sodium Salicylate, Theophylline, Theophylline and Sodium Acetate, Urea, Spirit of Nitrous Ether, Oil of Juniper, Scoparium, Saline diuretics	382-396
	Class B. Urinary Antiseptics: Hexamine, Hexyl Resorcinol, Mandelic acid, Copaiba, Oil of Sandal Wood, Buchu	396-403

GROUP	PAGE
Class C. Drugs used for Diagnostic Purposes :	
Uroselectan, Abrodil, Indigo Carmine . . .	403-404
XIV Drugs Acting on the Genital Organs . . .	404-406
Class A. Ecboics : Ergot, Histamine Acid Phosphate, Hydrastis, Pituitary . . .	406-421
Sex Glands . . .	421-425
Class B. Uterine Sedatives : Viburnum . . .	424-425
XV Antipyretics, Antiperiodics and Antiseptics . . .	
Antipyretics and Analgesics : Amidopyrine, Phenacetin, Phenazone, Acetanilide . . .	425-431
Antirheumatics : Salicylic Acid, Salicylates, Salicin, Benzoic Acid, Benzoates . . .	431-440
XVI Chemotherapeutic Agents . . .	440-442
Class A. Anti-malarial Remedies : Cinchona, Totaquina, Quinine, Quinidine, Plasmodochin, Atebrin . . .	442-464
Class B. Antisymphilitics : Mercury, Bismuth, Arsenic, Iodides . . .	465-505
Class C. Drugs used in Leishmaniasis Antimony Salts . . .	505-511
Class D. Drugs used in Trypanosomiasis Tryparsamide, Atoxyl, Bayer 205, Moranyl . . .	511-512
Class E. Drugs used in Amoebic Infection Acetarsol, Chiniofon, Carbarsone, Entero- Vioform, Rivanol . . .	512-514
Class F. Drugs used in Bacterial Invasion Sulphanilamide, Prontosil, Proseptasine, Soluseptasine, M. and B. 693 . . .	514-518
XVII Volatile Oils . . .	518-520
Class A. Turpentine Group . . .	
Oil of Turpentine, Oil of Pine, Colophony, Myrrh, Storax, Balsam of Peru, Balsam of Tolu, Oil of Cade . . .	520-526
Class B. Volatile Oils having Special Stimu- lating Effect on the Skin . . .	
Oil of Eucalyptus, Eucalyptol, Oil of Caju- put, Oil of Rosemary, Volatile Oil of Mus- tard, Capsicum . . .	527-531
Class D. Nauseants : Asafetida, Valerian . . .	531-533
Class E. Carminatives and Flavouring Agents : Clove, Oil of Clove, Cardamom, Caraway, Oil of Caraway, Coriander, Oil of Coriander, Dill, Oil of Dill, Oil of Anise, Lemon Peel, Fennel, Cinnamon, Oil of Cinnamon, Nutmeg, Oil of Nutmeg, Oil of Lavender, Oil of Peppermint, Ginger . . .	533-540
XVIII Solid Volatile Oils . . .	
Camphor, Menthol, Thymol . . .	540-546
XIX Antiseptics and Disinfectants . . .	546-547

CONTENTS

xiii

GROUP	PAGE
General Antiseptics and Disinfectants ..	547-548
1. Oxidising Agents: Hydrogen Peroxide, Potassium Permanganate ..	548-551
2. Halogens and their Compounds: Chlorinated Lime, Chloramine, Dakin's Solution, Iodine, Iodoform ..	551-558
3. Coal-tar Compounds: Phenol, Cresol, Resorcinol, Trinitrophenol, Prepared Coal Tar, Tar, Betanaphthol, Salol, Acriflavine, Fluorescein, Methylene Blue ..	558-571
4. Miscellaneous Compounds: Formaldehyde, Acetone, Boric Acid, Borax, Hydnocarpus Oil, Chaulmoogra Oil, ..	571-577
Parasiticides: Chrysarobin, Sulphur, Ichthammol ..	577-582
XX Nutrients	
Vitamins, Yeast, Ascorbic acid, Calciferol, Cod-liver Oil, Halibut-liver Oil, Sucrose, Lactose, Dextrose, Glucose, Lævulose, Gelatin, Lecithin ..	583-599
XXI Alteratives in Gout	
Guaiacum, Colchicum, Cinchophen, Neocinchophen ..	599-604
XXII Drugs Acting on Metabolism ..	604-606
Thyroid, Parathyroids, Insulin, Guanidine, Synthalin, Suprarenal Cortex, Thymus, Muscle Extract, Bone Marrow, Spleen ..	606-621
XXIII Drugs Acting on the Blood ..	621-627
Liver Extract, Desiccated Stomach, Iron ..	627-642
XXIV Drugs Acting on the Skin ..	642-644
Class A. Irritants and Counter-Irritants	
Cantharidin ..	644-649
Class B. Emollients and Demulcents	
Olive Oil, Sesame Oil, Cottonseed Oil, Almond Oil, Linseed, Arachis Oil, Glycerin, Honey, Liquorice, Acacia, Tragacanth, Starch, Soap, Paraffin, Oleic Acid, Lard, Suet, Beeswax ..	649-661
XXV Certain Diagnostic Agents ..	661
XXVI Drugs whose Actions are Mechanical: Pyroxylin, Collodion, Oil of Theobroma ..	661-662
XXVII Colouring and Sweetening Agents: Cochineal, Soluble Saccharin ..	663

PART IV VACCINE AND SERUM THERAPEUTICS

Immunity ..	664
Specific Antibodies ..	667
Specific Diagnosis ..	668
Bacteriophage Therapy ..	670
Serum Therapy ..	671
Antitoxic Sera ..	671
Antitoxinum Diphthericum, Toxinum Diphthericum Diagnosticum, Toxinum Diphthericum Calefactum, Toxinum Diphthericum Detoxicatum ..	672-675

	PAGE
Antitoxinum Tetanicum	675
Antitoxinum Edematiens, Antitoxinum Welchicum, Anti- toxinum Vibrio-septicum	676-677
Antitoxinum Staphylococcicum	677
Serum Antidysentericum (Shiga)	677-678
Serum Antimeningococcicum	678
Antivenom Sera, Snake Venoms	678-679
Antibacterial Sera	679
Serum Antipneumococcicum I and II	680-681
Selavo's Serum for Anthrax	681
Antistreptococcic Serum	682
Normal Serum	682
Anaphylaxis, Allergy	682-683
Vaccine Therapy	683
Immediate effects of Vaccine	685
Varieties of Vaccine	686
Vaccinum Vaccinæ	687
Antityphoid-paratyphoid Vaccine	688
Antiplague Vaccine	688
Anticholera Vaccine	688
Antirabic Vaccine	689
Curative Vaccine	689
Wright's Staphylococcal Vaccine	690
Streptococcal Vaccine	690
B. pyocyaneus	690
B. coli Vaccine	690
B. dysenteriae Vaccine	690
D. gonococcus Vaccine	690
Pertussis Vaccine	690
Pneumococcus Vaccine	690
Tuberculinum Pristinum	691-693
Causes of Failure of Vaccine Therapy	693
Abuses of Vaccine Therapy	693
Protein Therapy	694-695

PART V. RADIATION THERAPY

Ultra-Violet Rays	696-698
Radium	698-700

✓ PART VI. INDIAN INDIGENOUS DRUGS

Adhatoda, Saussurea Lappa	701
Belæ Fructus, Turpeth, Kaladana	701-703
Purnarnava	703
Cubebæ	703-704
Berberis, Alstonia, Picrorrhiza	704-705
Betel Leaf, Oleum Ajowan, Psoralea Corylifolia	705-707
Myrobalan, Kurchi Bark	707
Butea Seeds, Cucurbitæ Semina, Embelia	708
Ispaghula, Agropyrum	709
Terminalia Arjuna	709
Azaduachta Indica	710

PART VII. PHARMACY AND DISPENSING

General Directions	711
Weighing and Measuring	712
Waters	713

CONTENTS

XV

	PAGE
Decoctions	713
Infusions	713
Emulsions and Mixtures	714
Suspending and Emulsifying Agents	715
Mixtures and Emulsions of Special Drugs	716-719
Pills	719
Excipients	720
Rolling, Cutting and Rounding of Pills	721-722
Pills of Special Drugs	722-724
Pill-Coating	724
Powders	725
Capsules and Cachets	726-727
Blisters	727
Plasters	728
Suppositories, Pessaries and Bougies	729
Suppositories and Bougies of Special Drugs	729
Tinctures	730
Lozenges	730
Ointments	731
Ointments of Special Drugs	732
Sterilisation	732-733
Appendix I	
Extract from the Rules for Regulating the Possession for Sale and the Sale of Poisons	734-737
Appendix II	
Contractions of Words and Phrases	738-739
Appendix III	
Alternative Preparations Sanctioned for use in Tropical, Subtropical and other parts of the British Empire	740
INDEX	741-763

PHARMACOLOGY MATERIA MEDICA AND THERAPEUTICS

PART I

MATERIA MEDICA, in its widest sense, means the description of *materials or agents* employed in the treatment of disease. But properly speaking, it includes the following branches:—

1. **Materia Medica proper** is the science which treats of the natural history, as well as physical and chemical characters, of drugs. The term **Pharmacognosy** is used as a synonym to **Materia Medica proper**.

2. **Pharmacy** is the science and art of preparing and combining drugs, so as to make them fit for administration. It can be divided again as follows:—

(a) **Extemporaneous Pharmacy** is the making up or the compounding of formulæ or prescriptions of medical practitioners. **Dispensing** refers to the mode of putting up, labelling, and despatching.

(b) **Official Pharmacy** consists in the preparation of drugs and formulæ according to such processes as are recognised by, or prescribed in, an official pharmacopœia. The **British Pharmacopœia** is the Official Pharmacopœia of the British Empire.

3. **Pharmacology** is the science which describes the action of drugs on the general system, or on the individual parts of the body, in health. **Pharmacodynamics** is but another name for **Pharmacology**. It has been the custom of late to use the term **Pharmacology** in the same wide sense as **Materia Medica** was formerly used.

Toxicology or the toxic action of drugs comes under **Pharmacology**. It treats of the actions of drugs when given in doses large enough to endanger life.

4. **Therapeutics** relates to the remedial measures employed in the treatment of disease. It may be either **empirical or rational**.

(a) **Empirical Therapeutics** means the treatment of disease from experience only, and conforms to no pharmacological law yet known. In empirical treatment no explanation can be given for the success or otherwise of the use of a particular drug for a particular disease. We merely prescribe a certain drug because it has been found successful in a certain disease. A familiar example is the use of colchicum in gout. With our improved knowledge on the

action of drugs and the pathology of the diseases, we can explain the actions of many drugs that were used empirically before. Thus, we can explain the action of mercury in syphilis which was formerly used purely empirically.

(b) **Rational Therapeutics.**—By rational treatment we mean a mode of treatment suggested by our knowledge of the chemistry, physiology, and pharmacology of a given drug. Thus, when we prescribe $\frac{1}{100}$ gr. of atropine sulphate to check the night-sweats of phthisis we can explain (see *Belladonna*) how the perspiration is controlled. The uses of chloral hydrate for checking tetanic convulsions, and of digitalis for the cure of cardiac dropsies, are other instances of rational therapeutics.

Accessory Therapeutics—By accessory therapeutics is meant the treatment of disease, not by administration of drugs, but by other methods; such as, change of climate, regulation of food, clothing, exercise, baths, massage, and the like.

Chemotherapy.—Pharmacology is concerned with the physiological action of drugs and forms only a basis for the relief of symptoms rather than the cure of disease. Drugs like digitalis, adrenaline, pituitrin, etc., do not remove the underlying causes of the disease, although by relieving some urgent symptoms they remove the cause of distress and often act as curative agents. It is, however, in cases of diseases caused by micro-organisms or other parasites, that drugs may act purely as curative agents, and this specific treatment of infection by artificial remedies is known as *chemotherapy*, e.g. treatment of syphilis by organic arsenic preparations, of amœbic dysentery by emetine, and of malaria by quinine. The term was originally used by Ehrlich to mean parasitocidal treatment of infections by chemical agents. Since certain dyes are able to stain specifically certain cellular elements, a search was made to find substances which would unite with and destroy the parasitic agents of the disease without injuring the cells of the body, i.e. possess a maximum parasitotropic effect and a minimum organotropic property. But substances which are toxic to the parasites are also to a certain degree toxic to the body tissues. The object of chemotherapy, therefore, is to find substances which the tissues will stand in large doses, but will be fatal to the infecting organism in small doses, i.e. will have a favourable chemotherapeutic index, which is

$$\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}}$$

The greater the index, the greater will be its value.

The different ways in which these drugs act have been described under “Chemotherapeutic Agents.” It is necessary to point out that the co-operation of the tissues of the

host is an important factor and that the reticulo-endothelial system plays a prominent part in determining the action of a particular drug in a particular infection.

With the growth of our knowledge regarding the causation of the different infections and the progress of synthetic chemistry, newer remedies are being daily introduced which give promising results, so that remedies which were classed as specifics cease to be so in the presence of the many newer drugs which approach more towards specific action. In fact the word specific is used to mean that a particular preparation is more toxic to one particular parasite than on another or nearly related one.

MATERIA MEDICA PROPER

DRUGS

By "crude drugs" are meant the commercial forms of the animal or vegetable drugs as are brought to the market and utilised for the preparation of different medicinal products. Their value depends upon the presence of more or less definite chemical bodies known as "active constituents." These constituents are found in different parts of the plant, so that that particular part is used as the crude drug. Sometimes, however, they are found in all parts of the plant. In other instances no part of the plant is used as crude drug; for instance *aloe*, where the juice of the leaves contains the active constituent and forms the crude drug.

A. **Source.** - Drugs may be divided, according to their source, into the following groups:—

1. *Inorganic*.—This includes metals, salts, mineral acids, non-metals, like sulphur, etc.

2. *Organic*. - (a) From the *vegetable kingdom*, these form a large class. They are derived from roots, leaves, bark, wood, flowers, seeds, and the juice or exudates. (b) From the *animal kingdom*, these include different gland extracts, hormones, etc.

3. *Synthetic*.—As chloroform, chloral, ether, amyl nitrite, etc. Some of these drugs are gradually replacing organic ones; thus the synthetic salicylic acid is being used for the natural salicylic acid derived from the oil of wintergreen.

B. **Habitat.** - By habitat is meant the natural abode or locality of a plant or animal from which a drug is obtained.

C. **Collection.** - The medicinal activity of a drug depends greatly upon the habitat and the season of the year when it is gathered. Thus, rhubarb is useless until it is six years old. China and Turkey rhubarb are richer than those grown in India. The old cinchona bark is richer in quinine than the new.

COMPOSITION OF DRUGS

Inorganic drugs have a definite composition, which is well expressed by their names and chemical formulæ. The composition of organic drugs on the other hand is always complex and is ascertained after considerable analytical labour. They consist chiefly of acids, bases, salts, albuminous substances, alkaloids, balsams, cellulose, colouring matters, extractive matters, ferments, glycosides, gums, gum-resins, neutral principles, fixed and volatile oils, oleoresins, starch, sugar, etc. Some of them require a brief explanation.

Alkaloids are the active nitrogenous principles formed for the most part in the tissues of plants or animals. They may occasionally

be prepared synthetically. According to Hale-White, their characteristics are as follows:—

- “(1) They are the active nitrogenous principles of organic bodies.
- “(2) They are compound ammonias; that is to say, one or more atoms of hydrogen in ammonia (NH_3) are replaced by various radicals.
- “(3) They combine with acids to form crystalline salts without the production of water.
- “(4) They are alkaline, turning red litmus paper blue.
- “(5) A few are liquid, such as pilocarpine, coniine, nicotine, sparteine, lobeline. Liquid alkaloids nearly always contain only carbon, hydrogen and nitrogen.
- “(6) The solid ones are colourless, crystalline, and contain oxygen.
- “(7) They are sparingly soluble in water, readily so in alcohol. The salts are usually soluble in water.
- “(8) The solutions of many are intensely bitter.
- “(9) Most of them are closely related to pyridine, and some may be synthetically prepared from pyridine bases.”

The following alkaloids or their salts are official:—

Atropine	Codeine	Physostigmine
Caffeine	Morphine	Quinine
Cocaine	Pilocarpine	Strychnine

It should be noted that the names of alkaloids in Latin terminate in *ina*, and in English in *ine*. As *Atropina* (Latin), *Atropine* (English).

Vegetable alkaloids occur in almost all parts, but are most abundant in the seeds and roots, especially of dicotyledonous plants. A few are found in the lower plants, *e.g. muscarine* and *ergotoxine*. *Bases* found in the animal kingdom are commonly known as leukomains and ptomaines. The former are produced by the body cells and are products of metabolism, *e.g. adrenaline*, while the latter result from microbial decomposition of dead material, especially the amino-acids. These *bases* are known as *amines*, and are derived from ammonia by replacing H by alkyl groups.

Some plants contain many alkaloids, *e.g. cinchona*. In others one alkaloid is found in one part of the plant and another in a different part of the same plant.

Alkaloids are also prepared artificially, *e.g. theophylline*, *suprarenine*. Other artificial alkaloids are apomorphine prepared from morphine; homatropine, etc.

Incompatibles.—(a) *Alkalies*, which precipitate the less soluble pure alkaloid.

(b) *Tannin*, forming insoluble tannates.

(c) *Iodides* and *bromides*, forming insoluble iodides or bromides, or double salts.

(d) *Mercuric chloride*, forming insoluble double salt.

✓ Acids are salts of hydrogen. Numerous organic acids are found in plants, either in combination with inorganic bases such as potassium or calcium, or in a free state. Acids and their salts are of great pharmacological interest. Citric acid, tartaric acid, benzoic acid, salicylic acid, and mineral acids are some of the acids of the B. P.

✓ Bases are substances which react with acids and form salts. They are of two kinds:—(a) *Elementary*, to which metals belong. (b) *Compound*, such as ammonium and the alkaloids.

✓ Salts are compounds of acids and bases.

Neutral principles are indifferent crystalline proximate principles which are neutral and whose chemical composition is not known. They resemble alkaloids in action. The most important are the *glycosides*. Other neutral principles of value are aloin, *santonin*, *picrotoxin*, *quassin*, etc. Many of them have a bitter taste, as *quassin*, and are called “*amroids or bitter principles*.”

Note—Whereas the names of all alkaloids end in “*ine*,” those of glycosides and neutral principles end in “*in*.”

Glycosides are colourless crystalline solids soluble in water and alcohol. They split up on hydrolysis into a reducing sugar and a non-sugar component called *aglucone*. They are found in plants and liberate sugar with acids and certain ferments. They are neutral or weakly acid, and contain carbon, hydrogen and oxygen, a few have nitrogen in addition, and one or two, sulphur. They differ greatly in their solubility in water and alcohol, being mostly insoluble in ether. Some are powerful poisons while others are almost inert. Most of these are laxorotatory and have slightly bitter taste. Salicin, jalapin, digitalin, digitoxin, senegin, strophanthin, glycyrrhizin are some of the glycosides. The term *glucoside* is applied only to those glycosides in which the sugar component is glucose.

✓ **Tannins** are substances found in many plants specially in the leaves and bark. They are non-nitrogenous. Some are glycosides and form a group of phenol derivatives. They are soluble in alcohol and water, have an astringent taste and give a bluish or greenish colour with iron salts. They are precipitated by lead acetate, albumin and alkaloids.

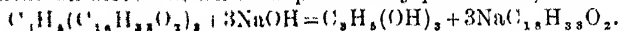
Saponins are non-nitrogenous substances generally glycosides, which emulsify oils and lase red blood-cells. On hydrolysis they yield sugar and a non-sugar component—*sapogenin*. They are neutral in reaction and form froth when mixed with water. The toxic ones are known as *sapotoxins*.

✓ **Enzymes or Ferments**.—These are a class of unstable bodies which produce chemical changes without apparently entering into the reaction or forming a part of the end products. They are destroyed at a temperature of 60° C. Examples of ferments are lactase, which converts lactose into glucose and galactose; myrosin which converts sinigrin of mustard seed into allyl-isothiocyanate; pepsin, trypsin, etc.

✓ **Hormones** are certain specialised substances having specific actions and are of extreme potency manufactured in specialised cells, notably those of the endocrine glands. Adrenaline, insulin, etc., are some of the hormones extensively used.

Oils of different kinds are used in medicine for a variety of purposes. They are fixed, and volatile.

A. Fixed Oils and Fats are mixtures of olein (liquid), palmitin (semisolid), and stearin (solid), with a small amount of other bodies in addition. They are found mostly in seeds, occurring within the cells as drops or crystals. They are insoluble in water, sparingly soluble in alcohol, freely in ether, chloroform, benzol, carbon disulphide and turpentine. With alkalies they form soap and glycerin, e.g. castile soap, which is made by the action of sodium hydroxide on olive oil, which is practically pure olein, thus:—



Oleate of Glyceryl	(Caustic Soda)	Hydrate of Glyceryl	Oleate of Sodium
or Olein		(Glycerin)	(Hard Soap)
(Vegetable Oil)			

Fats are fixed oils which remain solid at ordinary temperature, but differ from oils in the relative proportion of these basal ingredients, the fats having more of the stearin and palmitin, making them solid or semisolid, and the oils more of the liquid olein.

✓ **Characters of fixed oils:**

- They are non-volatile, and so leave a permanent grease spot;
- they cannot be distilled;
- they decompose under the influence of heat and become rancid;
- they are almost bland non-irritating substances (except croton oil) with nutrient and emollient properties; and

(e) they form soaps with alkalis.

A few of the fats and oils are of animal origin, *e.g.* butter, lard, suet and cod-liver oil, but the majority are of vegetable origin, as almond, linseed, olive and castor oils, and cocoa butter.

Castor oil and croton oil differ from the others in being soluble in alcohol and in possessing cathartic properties.

The *mineral oils* do not belong to this class of organic drugs. They are petroleum products, being mixtures of hydrocarbons, and do not become rancid.

Waxes are of firmer consistence than the fats, have a higher melting point, and cannot be saponified by boiling with an alkali.

B. Volatile Oils.—As plants often owe their characteristic odour to these oils they are often spoken of as *essential oils*. They contain a large number of preparations of diverse character and action. They are obtained by a process of distillation, except lemon oil, which is obtained by expression. They are found chiefly in the fruits and flowering parts of plants, or in the seeds and leaves. Owing to their strong characteristic odours they are largely used in perfumery, and to cover the taste and smell of nauseous drugs. As a rule they are clear, colourless liquids, some like cajuput and cubeb have peculiar greenish colour; cade, dark reddish-brown; and cinnamon oil, yellow and when old becomes reddish-brown. The commonest constituents are terpenes, sesquiterpenes and a few diterpenes. Terpenes are hydrocarbons of the aromatic series. In addition, they contain oxidised aromatic substances, as phenols and their derivatives, aromatic alcohols of the benzene series, and their corresponding aldehydes and ketones, aromatic alcohols of the camphor series, and sesquiterpene alcohol.

(a) They are volatile and can be distilled, and do not leave a permanent grease spot.

(b) They do not form soap with alkalis.

(c) They do not become rancid, but tend to resinify on exposure to light and air; and

(d) They are sufficiently soluble in water to impart to it their taste and odour.

Some of the volatile oils which are non-existent in the living plants are formed either by destructive distillation, or by the action of ferments on glycosides in the presence of water. The former are spoken as **Empyreumatic Oils**.

Bastedo has conveniently grouped the volatile oils as follows:—

- | | | |
|--|---|--|
| A. Existing in plant as such. | { | 1. Terpenes, $C_x H_x$ (oils of turpentine, juniper, etc.).
2. Terpenes + stearoptenes (oils of lemon, peppermint, etc.). |
| B. Not existing in plant as such, but developed from plant constituents. | { | 3. From enzyme action (oil of mustard).
4. Empyreumatic oils (oil of cade, oil of tar, creosote). |

In group 2 we have the mixtures of terpenes holding in solution oxygenated bodies of variable chemical nature. The terpene portion is known as *eleoptene*, the oxygenated portion as *stearoptene*. This stearoptene can be separated from the eleoptene by cold or fractional distillation, and is usually solid. They are therefore oxidised hydrocarbons of a crystalline nature, or solid volatile oils. The best known examples of stearoptenes are camphor, menthol and thymol.

Lipoids, Lipins, Lipides.—These are a group of substances resembling fats in their solubility in ether, alcohol, etc. They are widely distributed in the animal tissues chiefly nervous tissues. Lecithin and cholesterol are of interest to us.

Gums are colloidal carbohydrates which swelling or dissolving in water form viscid adhesive fluids known as *mucilage*. They are exudations from the stems, or branches, or both, of plants, and are composed of

- (1) *Arabin*, soluble in water; as gum arabic
- (2) *Bassorin*, partially soluble in water; as tragacanth.
- (3) *Cerasin*, or insoluble gum.

Pectin or vegetable jelly occurs in some medicinal plants and is allied to gum.

Balsams. These are oleo-resins or resins containing either benzoic or cinnamic acid or both. *Benzoin*, *balsam of Peru* and *tolu*, prepared *storax*, are the balsams of the B.P. Copaba and Canada balsam do not come under this group, though they are named balsams.

Resins are solid, brittle, non-volatile complex substances derived from the oxidation of volatile oils. They are soluble in alkalies forming resin soaps, and in alcohol, but insoluble in water. The resins of the B. P. are colophony, scammony, and podophyllin. When they are found dissolved in volatile oils they are known as **oleo-resins**, e.g. copaba, canada turpentine. Sometimes they are found in combination with gums and volatile oils, and are then known as **gum-resins**. They form emulsions when mixed with water. Ammoniacum and asafoetida are examples of gum-resins.

IMPURITIES OF DRUGS

1. **Imperfect Selection.**—This is due to the ignorance of collectors of crude vegetable drugs, who are imperfectly acquainted with their botanical characters and therefore fail to distinguish them from allied species; hence the substitution of an inferior or allied article for the genuine one.

2. **Imperfect Preservation** is one of the causes of deterioration of many drugs. Several drugs are materially affected by light and air, others by the lapse of time. Deliquescent salts and scale iron preparations quickly undergo physical change unless they are kept in carefully stoppered bottles. Syrupus Ferri Iodidi and Easton's Syrup are decomposed by light. Ergot, unless carefully dried and packed in an air-tight receptacle, soon becomes mouldy and loses strength. All extracts deteriorate unless put securely in sealed pots.

3. **Imperfect Preparation.** Impurities are of two kinds, (a) those which exist in the crude drug, (b) those which arise as by-products during the process of manufacture. They can be avoided only by scrupulous care on the part of the manufacturing pharmacists.

4. **Adulteration** is the intentional and fraudulent admixture of foreign substances with a drug. All highly priced drugs are liable to adulteration. Quinine is often adulterated, and Murrell mentions that once a large consignment of quinine was sent out to India containing not a trace of cinchona alkaloids.

THE BRITISH PHARMACOPEIA AND PHARMACEUTICAL PROCESSES

By a Pharmacopœia is meant a book published under the authority of a recognised body, generally constituted by law, for the purpose of securing uniformity of composition and strength of medicines used in the treatment of disease. The General Medical Council of the United Kingdom, authorised by the Medical Act of 1858, issues and revises from time to time the British Pharmacopœia. The first B. P. was published in 1864, and the last in 1932. One of the principal changes in the present edition is the introduction of the Metric System in the place of Imperial weights and measures. Other countries, as the United States, Germany, France, etc., also publish their own Pharmacopœias. Even hospitals have their own special pharmacopœias for speedy dispensing. Although the B. P. is the legal

standard, no medical man is bound to follow it. Drugs and preparations contained in the British Pharmacopœia are known as *official*.

The Council of the Pharmaceutical Society of Great Britain periodically publish a book called "The British Pharmaceutical Codex" which contains not only all the drugs and preparations of the British Pharmacopœia but also many other preparations not contained in it. The abbreviation of the British Pharmacopœia is B. P. C.

The following pharmaceutical processes are generally used:—

Bruising or Contusion is the process by which tough, hard and woody, soft, elastic and juicy substances are smashed or broken up in a roller-mill, or disintegrator, or on a small scale, in an iron mortar, so as to reduce them to a form suitable for being acted upon by a solvent, either by maceration, infusion, or decoction.

Calcination or Incineration is the operation by which drugs are exposed to a high temperature in order that watery and volatile matters may be driven off. This is best effected by putting the drugs in a crucible over a furnace.

Crystallisation is the process by which substances are made to assume the form of crystals.

Decoloration is the process by which we remove the colouring matters from alkaloidal substances, such as atropine, morphine, etc. This is effected by treating their solutions or mixtures with dried and purified animal charcoal, and subsequent filtration.

Despumation is the process by which an organic fluid is boiled until the impurities rise to the surface as scum, which is then removed by skimming or straining. Syrups made by this process keep longer.

Dialysis is the process of separating crystalloids from colloids by passing them through an animal membrane.

Digestion is a prolonged maceration at a temperature higher than that of the air.

Elutriation is the process by which a substance is pulverised and mixed with water, the coarser grains falling down to the bottom, while the lighter and finer ones are poured off with the water into another vessel, where deposition takes place slowly.

Expression is the process by which we press out juices and oils from vegetable substances, as in the preparation of succi, or squeeze out the liquid from the marc as in the preparation of tinctures. For this process suitable presses are required.

Fusion, Liquefaction or Melting is the process by which we melt or liquefy any solid body by heat. This is effected by putting it into a suitable vessel or crucible over a heated furnace, or on a water, steam or sand bath. We employ this process in the preparation of plasters, ointments, suppositories, caustic sticks, etc.

Granulation is the process by which a coarsely crystalline salt is converted into a granular powder by dissolving the former in water, and evaporating the solution to dryness with continuous stirring. Carbonate and citrate of potassium are made in this way.

Levigation is the pulverisation of a solid in the presence of water, or any other liquid which does not dissolve it; the finely comminuted particles being gathered with the washings and allowed to deposit slowly, whilst the coarser particles are again ground with the water or liquid, and so on, until the whole of the solid is reduced to a condition of fine powder.

Lixiviation means the separation of a soluble salt, from a mixed or compound solid, by dissolving the latter in water, decanting the supernatant liquid into another vessel, and evaporating it to dryness, leaving the insoluble residue behind. The solution is called a "*Lye*."

Maceration is the process of steeping a substance in alcohol, or some similar menstruum without the application of heat, in order to dissolve out its soluble matters. The insoluble residue is called the "*marc*."

Percolation is the process of extracting soluble matters by filtration of a liquid menstruum through a porous column of powdered material. A special apparatus, called a Percolator, is required.

Scaling is the process by which the scale preparations of drugs are made. It consists in spreading out in a thin layer, the concentrated solution of a drug on a glass, and allowing it to dry. The dried film is then separated and broken up. The scale ion preparations are made by this process.

Sifting is the method by which we separate finer powders from coarser ones by means of a sieve, which is made of either wire, horse-hair or muslin, of varying degrees of closeness. The B. P. directs a drug in No. 44, 60, 85, or 120 powder, and thereby means a degree of disintegration, as represented by the number of parallel wires in either transverse direction contained within the linear inch of a sieve.

When the soft pulp of fruits like figs, bael, prunes, or tamarinds is required to be sifted, the operation is called "**pulping**" which requires a great force in squeezing the pulp through the sieve.

Solution implies dissolving a solid into a liquid whereby the molecules of the solid disperse themselves into the liquid in such a way that no solid portion can be distinguished. This is *simple solution*, the change being physical. It is generally effected by putting the solvent in contact with the substance to be dissolved, and is often hastened by heat. The liquid which dissolves the solid is called the *solvent*. Ordinarily, as happens in simple solution, a solvent is capable of dissolving only a limited amount of a given solid, but when a solvent dissolves as much of the solid as it can contain, the solution is called a *saturated solution*. If saturated solution is made at a high temperature, the solid so dissolved in excess of saturation, may under certain conditions remain in solution at a lower temperature, when it is called *supersaturated solution*. But the excess of solid so dissolved separates and crystallises out on cooling.

Sublimation is the operation by which a solid is first vaporised by heat, and then the vapour is condensed as a deposit on the surface of another vessel, either *en masse*, in which case it is called a *sublimate*, as corrosive sublimate, or in a small feathery pulverulent state, known as *flowers*, as flowers of sulphur.

WEIGHTS AND MEASURES OF THE BRITISH PHARMACOPŒIA

METRIC SYSTEM

MEASURES OF MASS (WEIGHTS)

- | | |
|----------------------------|---|
| 1 Kilogram (kg. or kilog.) | is the Standard or International Kilogram |
| 1 Gramme (gm.) | = the 1000th part of 1 kilogram |
| 1 Milligram (mg.) | = the 1000th part of 1 gramme |
| 1 Microgram (γ) | = the 1000th part of 1 milligram |

For the purpose of writing prescriptions, in order to avoid the possibility of confusion between 'gramme' and 'grain', the symbol 'G.' should be used as the contraction for 'gramme'.

MEASURES OF CAPACITY (VOLUMES)

- 1 Litre (lit.) is the volume occupied by the mass of 1 kilogram of water at the temperature of its maximum density.
- 1 Millilitre or Mil (mil.) = the 1000th part of 1 litre.
- 1 litre measures about 1000.028 cubic centimetres.

MEASURES OF LENGTH

- | | |
|--------------------|--|
| 1 Metre (m.) | is the Standard or International Metre |
| 1 Centimetre (cm.) | = the 100th part of 1 metre |
| 1 Millimetre (mm.) | = the 1000th part of 1 metre |

- 1 Micron (μ) = the 1000th part of 1 millimetre
 1 Millimicron ($m\mu$) = the 1000th part of 1 micron

IMPERIAL SYSTEM

MEASURES OF MASS (WEIGHTS)

- 1 Pound (Avoir.) (lb) is the Standard Pound as defined in the Weights and Measures Act, 1878, Section 13
 1 Ounce (Avoir.) (oz.) = the 16th part of 1 pound = 437.5 grains
 1 Grain (gr.) = the 7000th part of 1 pound

MEASURES OF CAPACITY (VOLUMES)

- 1 Pint (pt.) is the Imperial Standard Pint as defined in the Weights and Measures Act, 1878, Section 15.
 1 Fluid Ounce (fl. oz.) = the 20th part of 1 pint = 8 fl. dr.
 1 Fluid Drachm (fl. dr.) = the 8th part of 1 fluid ounce = 60 min.
 1 Minim (min.) = the 60th part of 1 fluid drachm.

RELATION OF CAPACITY TO MASS (IMPERIAL)

- 1 Minim = the volume at 16.7° (62° F.) of 0.9114583 gr. of water
 1 Fluid Drachm = the volume at 16.7° (62° F.) of 54.6875 gr of water
 1 Fluid Ounce = the volume at 16.7° (62° F.) of 1 oz. or 437.5 gr. of water
 109.7143* Minims = the volume at 16.7° (62° F.) of 100 gr. of water

In the B.P. "per cent." is used to mean the following:—

Per cent. w/w = weight in weight.

Per cent. w/v = weight in volume.

Per cent. v/v = volume in volume.

RELATIONS OF METRIC AND IMPERIAL MEASURES

Mass

- 1 Kilogram (kg. or kilog.) = 15,432.3564 grains, or 35.274 ounces nearly, or 2.2046 pounds nearly
 1 Gramme (grm.) = 15.4323564 grains
 1 Milligram (mg.) = 0.015 grain nearly
-
- 1 Pound (Avoir.) (lb.) = 453.59 grammes nearly
 1 Ounce (Avoir.) (oz.) = 28.350 grammes nearly
 1 Grain (gr.) = 0.0648 gramme nearly

Capacity

- 1 Litre (lit.) = 1.75980 pints, or 35.196 fluid ounces nearly
 1 Millilitre or Mil (mil.) = 16.9 minims nearly
 1 Pint (pt.) = 568.2454 mls nearly, or 0.5682 litre nearly
 1 Fluid Ounce (fl. oz.) = 28.4123 mls nearly
 1 Fluid Drachm (fl. dr.) = 3.5515 mls nearly
 1 Minim (min.) = 0.0592 mil nearly

* Taken as 110 minims throughout the Pharmacopœia

	<i>Length</i>	
1 Metre	(m.)	= 39.370113 inches
1 Centimetre	(cm.)	= 0.39370 inch
1 Millimetre	(mm.)	= 0.039370 inch
1 Micon	(μ)	= 0.00003937 inch

1 Inch	(in)	= 25.3999 millimetres
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TABLE OF APPROXIMATE EQUIVALANCES ADOPTED IN STATING DOSES (IMPERIAL AND METRIC) IN THE BRITISH PHARMACOPEIA

Mils Grammes	Minims Grains	Mils Grammes	Minims Grains
10	150	0.3	5
8	120	0.25	4
6	90	0.2	3
5	75	0.15	2½
4	60	0.12	2
3	45	0.1	1½
2.6	40	0.08	1¼
2	30	0.06	1
1.6 or 1.5	25	0.05	¾ or ⅔
1.2 or 1.3	20	0.04	⅔
1	15	0.03	½
0.8	12	0.025	⅔
0.6	10	0.02	⅔
0.5	8	0.016	⅔
0.4	6	0.012	⅔

Gramme	Grain	Gramme	Grain
.01	⅓	.001	⅓ or ⅓
.008	⅓	.0008	⅓
.006	⅓	.0006	⅓
.005	⅓	.0005	⅓
.004	⅓	.0004	⅓
.003	⅓	.0003	⅓
.0025	⅓	.00025	⅓
.002	⅓	.0002	⅓ or ⅓
.0015	⅓	.00015	⅓
.0012	⅓	.00012	⅓

STANDARDISATION OF DRUGS AND
BIOLOGICAL ASSAY

Standardisation is the method adopted to obtain a definite uniformity in the strength of certain preparations containing active or alkaloidal principles, such as the extract of nux vomica, tincture of strophanthus, etc. This may be accomplished by chemical or pharmacological methods, generally expressed as pharmaceutical assaying. This secures a means of measuring therapeutic activity and makes it possible to furnish uniform preparations. Drugs having a definite chemical composition can be standardised by means of chemical assay. This method is utilised for opium, belladonna, nux vomica, etc., where the active constituents can be isolated in the pure form. But quite a large number of drugs and their preparations cannot be assayed by chemical methods, either because their active ingredients are not known, or perhaps they cannot be isolated quantitatively in a pure form by any chemical methods. They are assayed by biological methods. The Pharmacopœia gives details of the methods to be followed in each case, and this should be consulted. The following are the principal methods.

1. *Toxic Method*.—Guinea pigs, frogs, cats or other animals are generally selected for this test, and the value of the drug or preparation is calculated on the amount required to cause the death of the animal.

2. The amount required to produce certain definite effects on the animals, *e.g.* cock's comb method for ergot.

3. The amount required to produce a definite effect on an isolated organ, *e.g.* effect of pituitary extract on isolated uterus.

4. The amount required to clear the peripheral blood of mice infected with trypanosomes within 24 hours.

According to the British Pharmacopœia the following preparations are biologically assayed:—

Neoarsphenamine and Sulpharsphenamine.—These must comply with the test for absence of undue toxicity and for therapeutic potency.

(a) *Absence of undue toxicity*.—The average lethal dose of the standard preparation is 7.2 milligrams per mouse weighing from 13 to 15 grms. If the toxicity of the sample does not exceed that of the standard preparation by more than 20 p.c., it passes the test. It is tested by giving intravenous injection of 0.3 mil of a 2 p.c. solution of neoarsphenamine (or 0.35 mil *subcutaneously* of sulpharsphenamine) to mice weighing 13 to 15 grms. If not more than two die within three days the sample passes the test.

(b) *Therapeutic potency*.—This should have a curative action not less than the standard preparation kept in the National Institute for Medical Research, London. 0.03 mgrm. per gm. of body weight when injected into a vein of moderately infected mice (100,000 to 500,000 of trypanosomes per c.c. of blood) will clear the peripheral blood of trypanosomes in 48 to 72 hours.

Sulpharsphenamine is injected *subcutaneously*.

Digitalis.—The International Unit is the activity contained in 0.08 gm. of the standard digitalis powder. (1) The *frog test* consists of making injections of suitable dilutions of the extract of standard preparation and of the sample into similar groups of frogs and determining the amount of extract in mils required to produce death by systolic standstill of the ventricle per 100 gm. frog within 24 hours. The potency is calculated by comparing with that of the standard the percentage mortality amongst the frogs.

(2) *Cat or guinea-pig test* is done by slowly injecting into a vein extract of special strength into anæsthetised animals and determining the amount required to arrest the heart. The potency is determined by dividing the average lethal dose of the standard preparation by the dose required of the sample preparation.

Strophanthus and Tincture of Strophanthus are standardised in the same way.

Insulin.—The standard preparation is the dry soluble insulin hydrochloride, prepared and kept in the National Institute of Medical Research and samples when injected into rabbits should produce the same percentage of reduction of blood sugar as the standard, *i.e.* ± 10 p.c.

Ten or twelve healthy rabbits, each weighing about 2000 gm., are kept without food for 20 hours preceding the test, and divided into two groups. Each rabbit of the first group gets 1 Unit of the standard preparation subcutaneously, while the second group gets 0.5 mil of the sample to be tested. The blood sugar is estimated from the blood of each rabbit drawn at the end of each hour for five hours, and the average fall of blood sugar noted. Three or four days later the same test is repeated but the rabbits which received the standard preparation receive the test sample and the batch which received the test sample receive the standard sample, and the average 'percentage blood sugar reduction' again tested.

The sum of the numbers for the percentage blood sugar reduction

for two days with the standard sample is divided by the sum of the percentage blood sugar reduction with the test sample, and the result multiplied by hundred represents the percentage activity of the sample being tested in terms of the solution of the standard preparation.

Pituitary (Posterior Lobe) Extract.—The International Unit is the activity of 0.5 mgrm. of the standard acetone extracted preparation. The activity is determined from the amount of extract required to produce equivalent contraction of isolated uterus of guinea-pigs weighing 170 to 270 grms. as soon as weaned, suspended in a bath containing special oxygenated saline.

Old Tuberculin.—The potency is tested by comparing the dose necessary to produce its specific toxicity in guinea-pigs or other animals infected with the *B. tuberculosis*, with the standard preparation necessary to give the same effect. The inflammatory reaction is produced after 24 hours.

Diphtheria Antitoxin.—Its potency is determined by comparing the dose necessary to protect guinea-pigs against the effect of a fixed dose of diphtheria toxin, with the dose of standard preparation of diphtheria antitoxin, necessary to give the same protection.

Gas-gangrene Antitoxin (Perfringens).—Its potency is determined by comparing the dose necessary to protect mice or other animals against the lethal effect of gas-gangrene toxin, with the dose of a standard preparation of gas-gangrene antitoxin (perfringens), necessary to give the same protection.

The same procedure is followed in determining the potency of Gas-gangrene Antitoxin (oedematiens or vibriion septique). For this purpose there are necessary, (a) the Standard preparation of Gas-gangrene Antitoxin (perfringens, oedematiens or vibriion septique), and (b) a suitable preparation of Gas-gangrene Toxin of any of the three varieties for use as a test toxin.

Anti-dysentery Serum.—The assay is done in the same way as other sera except that the standard preparation of anti-dysentery serum is used. The Unit is the specific neutralising activity for the *B. Dysenteriae* (Shiga), contained in such an amount of the standard preparation as the Medical Research Council may indicate.

Tetanus Antitoxin.—For the comparison of potency there are necessary (a) the standard preparation of tetanus antitoxin, and (b) a suitable preparation of tetanus toxin for use as a test toxin. The Unit is the specific neutralising activity for tetanus toxin, contained in the standard preparation. The potency of a sample is determined by comparing the dose of it, necessary to protect guinea-pigs or mice against the lethal effect of a fixed dose of tetanus toxin, with the dose of the standard preparation of tetanus antitoxin, necessary to give the same protection.

Staphylococcus Antitoxin.—The potency is determined by comparing the dose necessary to neutralise the specific hæmolytic, dermo-necrotic or lethal effects of staphylococcus toxin, necessary to give the same protection. For this purpose are necessary, (a) the Standard Preparation of Staphylococcus Antitoxin, (b) a suitable preparation of staphylococcus toxin for use as a test toxin.

Antipneumococcic Serum.—Both types viz. I and II are tested in the same way. This is done by comparing the doses necessary to protect mice against the lethal effect of *Diplococcus pneumoniae* (types I and II) with the doses of standard preparation of antipneumococcic serum (types I and II) necessary to give the same protection. For this purpose the Standard Preparation of Antipneumococcic Serum (types I and II) and a suspension of living, highly virulent *Diplococcus pneumoniae* (types I and II) are necessary.

Antirachitic Vitamin D.—The activity of vitamin D is determined by comparing its antirachitic activity with the standard preparation of Great Britain and Northern Ireland, kept in the National Institute of Medical Research and is expressed in Units per gramme.

Curative Assay.—About 20 young rats, weighing 40 to 60 grms. are fed for about three weeks on rachitogenic diet* and the degree of rickets determined by taking X-ray photographs. The rats are now divided into two groups, one group receive daily doses of 0.25 to 1 unit of the standard preparation, while the other group the preparation to be tested, for 10 to 14 days. After this the rats are killed and the extent of cure of rickets is estimated by means of X-ray photographs.

Prophylactic Assay.—About 20 young rats weighing from 40 to 50 grms. are fed on one of the rachitogenic diets for 4 to 5 weeks during which they are divided into two groups. Rats of one group receive daily dose of 0.025 to 0.1 Unit of standard preparation, while the other receive the preparation to be tested. At the end of the period the rats are killed, and corresponding bones are taken from every rat. The weight of the ash is determined for the two groups. The average percentage of the bone ash of the rats fed on the sample to be tested, against the same of the rats fed on the standard preparation, gives the strength of the preparation tested.

Vitamin A.—The activity of a preparation of vitamin A is determined by comparing its activity with that of the standard preparation of vitamin A, or with that of a subsidiary laboratory standard, the activity of which is known in terms of the Standard Preparation.

The Unit is defined as the specific activity contained in 0.6 microgram (0.6 γ) of the Standard Preparation of β . carotene.

Assay is made by one of the following methods, viz.—

(a) By increase in weight in rats which have ceased to grow on a diet deficient in vitamin A.

(b) By *Spectrophotometric Method*.—This method measures the amount of a substance having a certain physical property characteristic of vitamin A.

Vitamin B₁.—The activity is determined by comparing the antineuritic activity with that of the Standard Preparation of Antineuritic Vitamin (Vitamin B₁) by a suitable method. The Standard Preparation is kept in the National Institute for Medical Research. The Unit is defined as the specific antineuritic activity contained in 10 mg. of the standard preparation. The preparation is standardised by comparing the increase in weight of rats which have ceased to grow while receiving a diet deficient in Vitamin B₁.

Vitamin C.—This is standardised in the same way as vitamin B₁. The Unit is defined as the specific antiscorbutic activity contained in 0.05 mg. of the Standard Preparation.

Its activity is standardised by observing the changes in the histological structure of the teeth on diets deficient in vitamin C and by determining the amount of protection given by the preparation tested as compared with the standard preparation.

OFFICIAL OR PHARMACOPŒIAL PREPARATIONS

The official preparations are sometimes called Galenical, after the celebrated physician Galen, but this term is now a misnomer, as with the advance of pharmacy, many drugs have come into use which were unknown in Galen's days.

Few drugs can be administered in their natural state. They are either too nauseous, too bulky, or contain some

* Rachitogenic diet.—Ground yellow maize, whole wheat, each 33 p c., wheat gluten, gelatin, each 15 p c., calcium carbonate, 3 p c., sodium chloride, 1 p c., or

Ground yellow maize, 76 p c., wheat gluten 20 p c., calcium carbonate 3 p c., sodium chloride 1 p c.

principles which are injurious to life or health. They are, therefore, submitted to certain processes prescribed by the British Pharmacopœia, in order to render them fit for administration, and also to help their preservation and storing, so as to maintain an uninterrupted supply during all seasons of the year. In the following pages we have given all the official preparations of the B.P. of 1932 and Addendum 1936, in a tabular form, with their composition, strengths, doses, and in many instances, their actions and uses

Aceta.—These are solutions of drugs in acetic acid, not in Vinegar. There is only one in the B.P.

Acetum Scillæ.—Squill bruised 10 gms., acid acetic dilute 100 mls. Dose.—10 to 30 ms. or 0.6 to 2 mls.

Acida Diluta.—Diluted Acids are strong acids diluted with distilled water. They are seven in number.

Acidum	Preparation	Dose	Action and Uses
Aceticum Dil.	Acetic acid 182 G, water 818 G	30 to 60 ms. 2 to 4 mls	Refrigerant and diuretic
Hydrobromicum Dil.	A solution containing 10 p.c hydrogen bromide by wt	15 to 60 ms 1 to 4 mls	Sedative. Prevents cinchonism
Hydrochloricum Dil	Hydrochloric acid 313 G, water 687 G Contains 10 p.c HCl.	5 to 60 ms 0.3 to 4 mls	In acid dyspepsia, gastric troubles
Hydrocyanicum Dil	A solution containing 2 p.c of hydrogen cyanide by weight	2 to 5 ms 0.12 to 0.3 ml	Sedative A deadly poison In vomiting, painful gastric disorders, &c
Hypophosphorosum Dil.	Barium hypophosphite and dilute sulphuric acid 10 p.c hypophosph acid.	5 to 15 ms 0.3 to 1 ml.	
Phosphoricum Dil.	Phosphoric acid 112 G, water 888 G	5 to 60 ms 0.3 to 4 mls	Tonic, refrigerant
Sulphuricum Dil	Sulphuric acid 104 G, water 896 G	5 to 60 ms 0.3 to 4 mls	Tonic, astringent To check diarrhoea

The dosage of all varies from 5 to 60 ms.; except—Acid. Hydrocyanicum Dil., 2 to 5 ms.; Acidum Hydrobromicum Dil., 15 to 60 ms.; Acidum Hypophosphorosum Dil., 5 to 15 ms., and Acidum Aceticum Dil., 30 to 60 ms.

Adeps and Adeps Lanæ. Lard and Wool Fat. Two preparations, as follows:—

Adeps Benzoinatus.—Lard 1000 gms., powdered benzoin 30 gms. Melt the lard in a water-bath, mix and strain.

N.B. In India suet should be used in place of lard.

Adeps Lanæ Hydrosus. *Syn.*—*Lanolin.*—Wool fat 7 gms., distilled water 3 mls. Mix by trituration in a warm mortar

Aquæ. Waters.—With the exception of distilled water, sterilised water, and Aq. Chloroformi all aquæ are weak and simple solutions of volatile oils obtained as described under aromatic waters. They are nine in number.

Aqua	Preparation	Dose	Action
Anethæ Conc	Oil of dill 2 mls, alcohol (90 p.c.) 60 mls, water q.s. to 100 mls	5 to 15 ms (0.3 to 1 ml)	Carminative
Anethæ Dest	Dill 10 gm, water 200 mls, distil 100 mls.	$\frac{1}{2}$ to 1 oz (15 to 30 ml)	Do
Camphoræ	Camphor 1 gm, alcohol (90 p.c.) 2 mls, and distilled water 1000 mls By solution	$\frac{1}{2}$ to 1 oz (15 to 30 ml)	Stimulant and antispasmodic. As a vehicle

Aqua	Preparation	Dose	Action
Chloroformi	Chloroform 25 mls, distilled water to 1000 mls by solution	$\frac{1}{2}$ to 1 oz. (15 to 30 ml)	A flavouring agent
Cinnamomi Conc	Cinnamon oil 20, alcohol (90 p c) 600, water q.s. 1000	5 to 15 ms (0.3 to 1 ml)	Carminative, flavouring agent
Cinnamomi Dest	Cinnamon bruised 1 gm and water 20 mls, distilled 10 mls	$\frac{1}{2}$ to 1 oz. (15 to 30 ml)	A carminative
Destillata	Distilled from natural potable water	..	A vehicle
Menthae Pip. Conc.	Peppermint oil 20, alcohol (90 p c,) 600, water q.s. 1000	5 to 15 ms. (0.3 to 1 ml)	An antispasmodic and carminative vehicle.
Menthae Pip. Dest	Oil of peppermint 1 ml and water 1500 mls., distilled 1000 ml	$\frac{1}{2}$ to 1 oz (15 to 30 ml)	Do

Aquæ Aromaticæ.—Aromatic waters are prepared either by (a) *distillation*, (b) *solution*, i.e. by shaking the essential oil with five hundred times its volume of distilled water for fifteen minutes and filtering after 12 hours; or by triturating the oil with powdered talc, keiselguhr, or pulped filter paper, and five hundred times its volume of distilled water, and filtering; or (c) by diluting the concentrated water with 39 times its volume of distilled water.

N.B.—Concentrated aromatic waters are weak alcoholic solutions of volatile oils which when diluted with 39 times its volume of distilled water, yield a preparation which is approximately equivalent to distilled aromatic water in strength, but contains about 1.5 p.c. ∇/∇ of alcohol (90 p.c.).

Aqua Sterilisata. *Sterilised Water.*—Distil potable water from a glass still, or a still in which the distillate does not come in contact with copper, which has been cleansed immediately before distillation. Reject the first portion and collect in a sterilised neutral glass container. Close the container to exclude bacteria, and immediately sterilise by heating in an autoclave.

Cataplasmata. Poulitices are thick pasty preparations intended for local application, either cold or hot. Only one preparation, viz.—

Cataplasma Kaolin. *Kaolin-Poultice.*—Kaolin (finely sifted) 527 grms., boric acid (finely sifted) 45 grms., methyl salicylate 2 mls., oil of peppermint 0.5 mil., thymol 0.5 grm., glycerin 425 grms.

N.B.—Should be kept in a well-closed container.

Collodia.—Collodions are solutions of drugs in collodion, or solution of pyroxylin in ether and alcohol.

Collodium Flexile.—Pyroxylin 2 gm., colophony 3 gm., castor oil 2 gm., alcohol (90 p.c.) 24 mls, ether q.s. to 100 mls. The alcohol (90 p.c.) may be replaced by industrial methylated spirit of the same strength.

Confectiones.—Confections, Electuaries or Conserves are soft preparations of drugs, made into a paste with sugar or honey, either to give them a pleasant and agreeable taste, or to preserve them. The dose of all confections is 60 to 120 grs. or 4 to 8 grms. There are only two in the B.P.

Confectio	Ingredients	Strength	Action and uses
Sennæ	Powdered senna leaf 10 grms, powdered coriander 4 grms, figs 16 grms., tamarind and cassia, each 12 grms, prunes 8 grms, extract of liquorice $1\frac{1}{2}$ grms, sucrose 40 grms, water q.s to 100 grms.	10 p c	A safe and elegant laxative in chronic constipation.

Confectio	Ingredients	Strength	Action and uses
Sulphuris	Precipitated sulphur 450 gms, acid pot tate 110 gms, tragacanth 5 gms, syrup 210 mls, tincture of orange 55 mls, glycerin 170 mls	45 p c	A gentle laxative.

Effervescent Granular, or those preparations that effervesce when mixed with water. All are granular. They are prepared by the admixture of acids and alkalies. **Pulvis Effervescens Compositus** (*Seidlitz Powder*) is described under powders.

The following are the B P. granular effervescing preparations, the quantities of which are given in grammes :—

Effervescent	Composition	Dose	Action and uses
Sodium Phosphate	Sodium phosphate 50, sod bicarb 50, tartaric acid 24, citric acid 21	60 to 240 grs (4 to 16 gms)	A mild aperient.
Sodium Sulphate	Sod bicarb 50, sod. sulph 50, tartaric acid 24, citric acid 21	60 to 240 grs (4 to 16 gms)	Hydragogue purgative.

Elixiria. Elixirs are weak tinctures of drugs rendered pleasant and agreeable by admixture of sugar and aromatics. Only one in the B P., viz.—

Elixir Cascaræ Sagradæ.—Cascara sagrada in coarse powder 1000 grms., liquorice, unpeeled, in coarse powder 125 grm., light magnesium oxide 150 grms., soluble saccharin 1 grm., oil of coriander 0.15 mil, oil of anise 0.2 mil., alcohol (90 p.c.) 125 mls., glycerin 300 mls., distilled water, q s. to 1000 mls. *Dose.*—2 to 4 mls or 30 to 60 ms.

Emplastra. Plasters.—Four in number. They are made of adhesive substances spread upon cloth or leather so as to adhere to the skin. They are applied for the purpose of holding medicinal substances in contact with the body, of acting as a protective and support, or of bringing the edges of a wound together.

Emplastrum	Materials used	Strength	Action and uses
Belladonnæ	Powdered root percolated with alcohol and water to make an extract. Mix with colophony plaster to required strength	0.25 p.c of alkaloids	A local anodyne. In lumbago, neuralgia, swollen and painful glands
Cantharidini	Cantharidin 2 gm., acetone 100 ml, castor oil 200 gm., yellow bees-wax 400 gm, wool fat 398 gm	0.2 p c of cantharidin	Vesicant.
Colophonii	Colophony 10 gm., lead plaster 85 gm, hard soap 5 gm	10 p c.	For strapping wound.
Plumbi	Lead monoxide 4 gms, olive oil 8 gms., water 4 mls. or q s	.	Sedative and protective.

Extracta. Extracts.—These are prepared by extracting the active principles either with water, alcohol, or both, or with ether. They contain different active principles in a very concentrated form with very little inert substance. Different methods are used for extraction, viz., *maceration, infusion, percolation* and *decoction*. According to

the consistency of the different extracts they have been divided into, Dry or Solid, Semisolid or Soft, and Liquid.

The B.P. directs that the industrial methylated spirit of equivalent strength may be substituted in place of alcohol in the preparation of the different extracts provided no industrial methylated spirit is left in the finished product.

Of the different extracts, Ext. Fellis Bovini, Ext. Hepatis Liq., Ext. Hepatis Sic., and Ext. Pituitarii Liq., are animal products.

Semisolid or Soft Extracts are prepared by dissolving, macerating, infusing or boiling drugs in cold or hot distilled water, and evaporating the solution, infusion or decoction, as the case may be, to the consistence of a soft extract. They are six in number.

Extractum	Source	Process	Menstruum	Dose
Cinchonæ	Cinchona 1000 gm, glycerin, and alcohol q s (4% alkaloids in 8 gis)	P & E	Alcohol	2 to 8 gr. (0.12 to 0.5 G)
Fellis Bovini	Ox gall	E	Alcohol	5 to 15 gr. (0.3 to 1 G)
Gentianæ	Sliced root dried	M D & E	Water	2 to 8 gis (0.12 to 0.5 G)
Glycyrrhizæ	Dried root	M D & E	Chloroform water	10 to 30 gis (0.6 to 2 G.)
Malti	Malted grain of barley	Digestion & E	Water	60 to 240 ms (4 to 16 ml)
Maltic Oleo Morrhuzæ	Malt extract 9 G, Cod-liver oil 1 G (15% Cod-liver oil)		. .	60 to 240 ms. (4 to 16 ml)

Except Extractum Cinchonæ which has been diluted with glycerin to contain $\frac{1}{2}$ gr. of total alkaloids in 8 grs., the strengths of the soft extracts are not adjusted, but since they do not contain any potent principle this is of little consequence.

Liquid Extracts are prepared from drugs with water as the solvent and about 20 p.c. alcohol is added for their preservation against fermentation and fungoid growth. Ext. Cinchonæ Liq. is prepared from soft extract. They are fifteen in number.

Extractum	Ingredients	Alcohol p c in the menstruum	Strength	Dose
Belladonnæ Liq	Belladonna root, alcohol, water	90	0.75 p c alkaloids	$\frac{1}{4}$ to 1 m 0.015-0.06 ml.
Cascariæ Sag Liq	Cascara powder 1000 G, alcohol 250 ml., water q s to 1000 ml	90	50 p c	30 to 60 ms 2 to 4 mls
Cinchonæ Liq	Ext cinchon 50 G, hydrochloric acid 3 ml., glycerin 10 ml., alcohol 25 ml., water q s to 100 ml	90	5 p c alkaloids	5 to 15 ms 0.3 to 1 ml
Colchici Liq.	Colchicum seed 1000 G, alcohol q s 1000 ml.	60	0.3 p c colchicine	2 to 5 ms 0.12 to 0.3 ml
Ergotæ Liq	Ergot 1000 G., tartaric acid, alcohol, each q s	50	0.06 to 0.04 p c ergotoxine	10 to 20 ms. 0.6 to 1.2 ml
Glycyrrhizæ Liq	Liquorice 1000 G, chloroform water and alcohol q s.	90	Sp gr 1.200	30 to 60 ms 2 to 4 mls

D=Decoction. E=Evaporation. I=Infusion P=Percolation M=Maceration.

Extractum	Ingredients	Alcohol p c in the men- struum	Strength	Dose
Hamamelidis Liq.	Hamamelis 1000 G, alcohol q s to 1000 ml	45	50 p c	30 to 60 ms. 2 to 4 ml.
Hepatis Liq	Liver of ox or sheep, glycerin, alcohol, water	95	1 oz equal to 8 oz fresh liver	1 oz 30 mls
Hyoscyami Liq	Hyoscyamus powder 1000 G., alcohol q.s	70	0.05% of alkaloids	3 to 6 ms 0.2 to 0.4 ml.
Ipecacuan- hæ Liq.	Ipecac powder 1000 G., alcohol q.s	90	2 p c emetine	$\frac{1}{2}$ to 2 ms. or 10 to 30 ms.
Nucis Vomicæ Liq.	Nux vomica 1000 G, alcohol q s	45 & 70	15 p c strychnine	1 to 3 ms 0.06 to 0.2 ml.
Pituitarii Liq.	Posterior lobe of pitui- tary of ox, water and acetic acid.	.	10 Units per mil	2 to 5 Units 0.2 to 0.5 ml. (subcutane- ously)
Senegæ Liq	Senega 1000 G., dilute solution of ammonia q s, alcohol q.s to 1000 ml	60	50 p c.	5 to 15 ms 0.3 to 1 ml
Sennæ Liq	Senna fruit 1000 G, alco- hol 250 ml, chloro- form water q s 1000 ml	90	50 p c	10 to 30 ms 0.6 to 2 mls
Stramonii Liq.	Stramonium 1000 G, alcohol q s	45	0.25 p c. hyoscyamine	$\frac{1}{2}$ to 3 ms. 0.03 to 0.2 ml

N. B.—Extract of male fern, extracts of malt and malt with cod liver oil are thick viscid liquids, though they are not called liquid extracts in the B.P.

From the above table it will be gathered that all the liquid extracts, except pituitary, require alcohol of various strengths, either for their preparation or for their preservation. Extract of Male Fern being prepared with ether is given in the table of **Ethereal Extracts**.

In the preparation of liquid extract of colchicum, the seeds are first treated with light petroleum to remove fat before adding alcohol; while ergot is treated with light petroleum to remove fat and then the liquid extract is prepared with alcohol acidified with tartaric acid; and pituitary extract with distilled water acidified with acetic acid.

The *strength* of liquid extracts not containing any potent principle is so adjusted that one part by weight of the drug produces one part by volume of the finished product, *i.e.* the strength is 1 in 1. In the case of extracts of powerful drugs, the strength is adjusted to a definite percentage of the active principle based on the average percentage of the active principle present in the crude drug. Thus the liquid extract of ipecacuanha is so adjusted that it should contain 2 p c. *emetine*, *i.e.* the alkaloid strength contained in ipecacuanha.

Ethereal Extracts are prepared by percolating dry drugs with ether. There is only one in the B.P.

Extractum	Ingredient	Process	Menstruum	Strength	Dose
Filicis	Male Fern	P.	Ether	25 p c Filicin.	45 to 90 ms 3 to 6 mls

Dry Extracts, sometimes called **abstracts**, are alcoholic or watery extracts mixed with an inert powdered substance and then dried and powdered. They are ten in number.

Extractum	Ingredients	Process	Strength	Dose
Belladonnæ Sic.	Belladonna leaves, alcohol 70 p.c.	P & E	1 p.c. Alkaloids	1/4 to 1 gr. 0.015-0.06 G.
Cascara Sagradæ Sic.	Powdered cascara sagrada and water	P. & E		2 to 8 grs. 0.12 to 0.5 G.
Colchici Sic.	Colchicum corm 1000 G., alcohol (60 p.c.) and lactose, each q.s.	P & E.	1 p.c. colchicine	1/4 to 1 gr. 0.015-0.06 G.
Colocynth Co.	Colocynth 27 G., aloes 56 G., scammony 18 1/2 G., cold soap powder 14 G., cardamom 4 1/2 G., alcohol (60 p.c.) 700 ml.	M & E	27 p.c.	2 to 8 gr. 0.12 to 0.5 G.
Hepatis Sic.	Trimmed ox oi sheep liver, alcohol (80 p.c.), sulphuric acid and water	E	...	Equivalent to 1/2 lb. of fresh liver
Hyoscyami Sic.	Hyoscyamus 1000 G., alcohol (70 p.c.) q.s.	P & E	0.3 p.c. alkaloid	1/4 to 1 gr. 0.016-0.06 G.
Krameria Sic.	Krameria, water	P & E	...	5 to 15 grs. 0.3 to 1 G.
Nucis Vomica Sic.	Nux vomica 1000 G., alcohol (70 p.c.), cal. phosphate each q.s.	P. & E	5 p.c. strychnine	1/4 to 1 gr. 0.015-0.06 G.
Opi Sic.	Opium, water, calcium phosph	E.	1/5 gr. morphine in 1 gr	0.015-0.06 G.
Stramonii Sic.	Stramonium, 1000 G., alcohol (95 p.c.), starch each q.s.	P. & E.	8/100 gr hyoscyamine in 8 gr	1/4 to 1 gr. or 1 to 8 grs

The following extracts are standardised:—

Ext. Belladonnæ Liq.	Ext. Hyoscyam. Sic.
" " Sic.	" Ipecac. Liq.
" Cinchonæ	" Nucis Vom. Liq.
" " Liq.	" " Sic.
" Colchici Liq.	" Opii Sic.
" " Sic.	" Pituitarii Liq.
" Ergot. Liq.	" Stramonii Liq.
" Hyoscyam. Liq.	" " Sic.

Because of the variations in the strengths of the different preparations, there is very little uniformity in the dosage of the different extracts. The student should however try to remember the maximum doses of the extracts containing powerful active principles

Names of extracts	Maximum dose
Belladonnæ Liquid.	1 minim
Ipecac. Liq.	2 ms.
Nucis Vomica Liq.	3 ms.
Stramonii Liq.	3 ms.
Colchici Liq.	5 ms.
Hyoscyami Liq.	6 ms.
Ergot. Liq.	20 ms.
Bellad. sic., Colchici sic., Hyoscyam. sic., } Nucis Vom. sic., Opii sic., Stramon. Sic. }	1 gr.

Gelatinum. Gelatin pastes are mixtures of gelatin, glycerin and water in varying proportions, and are non-irritating protectives to the skin. They should be melted before use and applied with a brush. There is only one preparation.

Gelatinum Zinci. *Syn.—Unna's Paste.*—Zinc oxide, gelatin cut small, each 150 grm., glycerin 350 grm., distilled water 350 mls or q.s.

Glycerina.—Glycerins are solutions of drugs in plain glycerin or glycerin and water. Because of the high viscosity of glycerin these preparations adhere to the mucous surface over which they are applied, therefore they are very popular as throat applications where

the demulcent action of glycerin also comes into play. Phenol having greater affinity for glycerin than water, Glycerinum Phenolis does not act as a caustic. They are six in number.

Glycerinum	Ingredients	Dose	Action
Acid. Borici	Boric acid 31 G., glycerin q s to 100 G	10 to 30 ms	Antiseptic.
Acid. Tannici	Tannic acid 15 G., glycerin 85 G	10 to 30 ms	Astringent.
Aluminis	Alum 13 G., water 6 mls, glycerin 81 G.	30 to 60 ms	Do
Amyli	Starch 85 G., water 170 mls, glycerin 745 G.	..	Emollient
Boracis	Borax 12 G., glycerin 88 G	30 to 60 ms	Antiseptic, emollient.
Phenolis	Phenol 16 G., glycerin 84 G	5 to 15 ms.	Antiseptic

Infusa Recens.—Fresh Infusions are watery solutions of vegetable principles, prepared by soaking in cold or boiling water, coarsely powdered or bruised crude drugs for a certain time in a covered vessel, and then straining the liquid. Quassia and calumba only are infused in cold water. The amount of water in all cases is 1000 mls. All infusions become inky with persalts of iron, except those of quassia and calumba. They should always be prepared fresh, and the prescriber should always specify “recens” when fresh infusion is required. To a student, the infusion of digitalis is most important, it contains 0.05 Unit of activity in 1 mil, and one-twentieth of the strength of the tincture. The dose is 6 to 20 mls or 90 to 300 ms. For a single dose it is given in 30 to 120 mls or 1 to 4 oz. They are nine in number.

For dispensing purposes, fresh infusion should be used within twelve hours of its preparation.

Infusum	Ingredients	Strength	Time in minutes	Dose
Aurantii Rec	Dried bitter-orange peel cut small 50 G., boiling water 1000 G	1 in 20	15	½ to 1 oz
Buchu Rec	Buchu leaves broken 50 G., boiling water 1000 G	1 in 20	15	1 to 2 oz.
Calumbæ Rec	Calumba 50 G., cold water 1000 ml	1 in 20	30	½ to 1 oz.
Caryophylli Rec.	Clove bruised 25 G., boiling water 1000 G	1 in 40	15	½ to 1 oz.
Digitalis Rec	Digitalis leaves powdered 4 G., and boiling water 1000 G.	0.05 Unit in 1 mil	15	90 to 300 ms. or 1 to 4 oz.
Gentianæ Co. Rec	Gentian root thinly sliced 125 gms., dried bitter orange peel cut small 125 gms., lemon peel small 25 gms., boiling water 1000 gms	1 in 80	15	½ to 1 oz.
Quassia Rec.	Quassia rasped 10 G., cold water 1000 mls	1 in 100	15	½ to 1 oz.
Senegæ Rec.	Senega powdered 50 G., boiling water 1000 G	1 in 20	30	½ to 1 oz.
Sennæ Rec.	Senna fruit 100 gms., ginger sliced 5 gms., boiling water 1000 gms	1 in 10	15	½ to 2 oz

Infusa Concentrata. Concentrated infusions are solutions of drugs in alcohol, prepared either by percolation or maceration, to be diluted

with seven times their volume of distilled water, when they become approximately equivalent in strength, but not in flavour, to fresh infusions, but containing only a small proportion of alcohol. They are eight in number.

N. B.—Infusions of senna, both fresh and concentrated, are now prepared with fruits and not with leaves as before.

Infusum	Ingredients	Process	Dose
Aurantii Conc.	Dried bitter orange peel 400 grm., alcohol (25 p.c.) 1350 mls	M	2 to 4 mls 30 to 60 ms
Buchu Conc.	Buchu freshly broken 400 grms, alcohol (25 p.c.) q.s 1000 mls	P	4 to 8 mls. 60 to 120 ms
Calumbæ Conc.	Calumba cut small 400 grm, alcohol (90 p.c.) 250 mls, distilled water q.s to 1000 mls.	M.	2 to 4 mls 30 to 60 ms
Caryophylli Conc.	Clove bruised 200 grm., alcohol (25 p.c.) 1100 mls	M	2 to 4 mls 30 to 60 ms
Gentianæ Compositum Conc	Gentian sliced 100 grm, dried bitter orange peel 100 grm., lemon peel 200 grm, alcohol (25 p.c.) 1200 mls	M.	2 to 4 mls. 30 to 60 ms
Quassia Conc	Quassia rasped 80 grm, alcohol (90 p.c.) 250 mls, distilled water q.s to 1000 mls	M	2 to 4 mls 30 to 60 ms.
Senegæ Conc.	Senega 400 grms, dilute solution of ammonia and alcohol (25 p.c.) each q.s. to 1000 mls	P.	2 to 4 mls 30 to 60 ms
Sennæ Conc	Senna fruit 800 grm, Strong t _l of ginger 80 mil, alcohol (20 p.c.) q.s to 1000 mls.	P	2 to 8 mls. 30 to 120 ms

Injectio. Injections are solutions or suspensions of drugs intended for injection into the muscle, except *Injectio Sodii Chloridæ et Acaciæ* which is meant for intravenous injection. They are eight in number.

Injectio	Ingredients	Strength	Dose
Bismuthi	Precipitated bismuth 20 grm., dextrose 5 grm., cresol 0.5 mil., sterilised water q.s to 100 mls.	3 grs in 15 ms.	0.5 to 1 ml. 8 to 15 ms.
Bismuthi Oxychloridi	Bismuth oxychloride 10 grm., dextrose 5 grm, cresol 0.5 mil, sterilised water q.s to 100 mls	3 grs in 30 ms.	1 to 2 mls 15 to 30 ms.
Bismuthi Salicylatis	Bismuth salicylate 10 grm, camphor, phenol, each 1 grm, olive oil q.s to 100 mls.	2 grs in 20 ms	0.6 to 1.2 mls. 10 to 20 ms
Ferri	Solution of ferric chlor 7 mls, citric acid 2 grm, dilute solution of ammonia and distilled water q.s, sterile water q.s to 100 mls	1/2 gr iron and ammon. cit or 1/10 gr iron in 30 ms	1 to 2 mls 15 to 30 ms
Hydrargyri	Mercury 10 grm, wool fat 50 grm, camphor 10 grm, creosote 10 mls, olive oil 23 mil	1 gr Hg in 10 ms	0.3 to 0.6 ml 5 to 10 ms
Hydrargyri Subchloridi	Calomel 5 grm, wool fat 50 grm, camphor 10 grm., creosote 10 mil, olive oil 23 mil	1 gr calomel in 20 ms	0.6 to 1.2 ml 10 to 20 ms
Mersalyli	Mersalyl 10 grm, theophylline 5 grm, sodium hydroxide 0.05 grm or q.s sterilised water q.s to 100 mls.	3 grs mersalyl, 1 1/2 gr theophylline in 30 ms	0.5 to 2 ml. 8 to 30 ms
Sodii Chloridi et Acaciæ	Sodium chloride 9 grm, acacia 60 grm, sterilised water q.s to 1000 mls	0.9 p.c	

Lamellæ.—Eye-discs are thin plates or discs of medicated gelatin with glycerin, used in ophthalmic practice. These are prepared by

Note.—M=Maceration. P=Percolation.

dissolving gelatin 18 gms., in glycerin 2 gms., and water 88 gms. or *q.s*. They are four in number.

Lamella	Composition	Strength in each	Action
Atropinæ	Discs of gelatin with glycerin weighing about $\frac{1}{50}$ gr. each	$\frac{1}{5000}$ gr	Mydriatic
Cocainæ	Discs of gelatin with glycerin weighing about $\frac{1}{50}$ gr. each.	$\frac{1}{50}$ gr	A local anæsthetic
Homatropinæ	Discs of gelatin with glycerin weighing about $\frac{1}{50}$ gr. each	$\frac{1}{100}$ gr	Mydriatic
Physostigminæ	Discs of gelatin with glycerin weighing about $\frac{1}{50}$ gr. each	$\frac{1}{1000}$ gr	Myotic

Linimenta.—Liniments or Embrocations are preparations used for rubbing or painting over the skin. The majority of them are limpid liquids. Camphor enters into their composition for its local stimulant action, and also to lessen the risk of these being taken internally as it has a characteristic strong smell. It must be remembered that Linimentum Terebinthinæ Aceticum should not be mixed with Linimentum Camphoræ Ammon. as by this admixture a chemical combination takes place which neutralises the effects of both the ammonia and acetic acid. They are seven in number.

Linimentum	Composition	Strength	Action and uses
Aconiti	Aconite 50 G., camphor 3 G., alcohol (90 p.c.) <i>q.s</i> 100 mls.	50 p.c.	A powerful local sedative and anodyne
Belladonnæ	Belladonna root 1000 G., camphor, alcohol (90 p.c.), water, each <i>q.s</i> to produce the required strength.	0.375 p.c. alkaloids	A powerful local anodyne in neuralgia, etc
Camphoræ	Camphor in flowers 2 G., and olive oil 8 G.	20 p.c.	A local stimulant
Camphoræ Ammoniatum	Camphor 125 gms., oil of lavender 5 mls., strong solution of ammonia 250 mls., and alcohol (90 p.c.) to 1000 mls	125 p.c.	Rubefacient and counter-irritant
Saponis	Soft soap 80 gms., camphor 40 gms., oil of rosemary 15 mls., alcohol (90 p.c.) <i>q.s</i> to 1000 mls., and water 170 mls.	8 p.c.	A stimulant application to sprains and bruises
Terebinthinæ	Soft soap 75 gms., camphor 50 gms., oil of turpentine 650 mls., water <i>q.s.</i> to 1000 mls	65 p.c.	Irritant and rubefacient
Terebinthinæ Aceticum	Glacial acetic acid 110 mls., liniment of camphor 445 mls., oil of turpentine <i>q.s</i> to 1000 mls	44 p.c.	Powerful rubefacient

Liquores—Solutions are solutions of vegetable, animal or inorganic substances in distilled water, either alone or with other solvents. Liqr. Adrenalini Hydrochlor and Liqr. Epispastici are obtained from the animal kingdom. Liqr. Epispasticus is prepared with acetone. Most of the vegetable solutions are made with the aid of alcohols of various strengths. They are thirty in number.

Liquor	Composition	Strength	Dose
Adrenalini Hydroch	Adrenaline 1 G., chlorbutol 5 G., sodium chloride 9 G., acid hydrochlor dil 3 ml., water <i>q.s</i> to 1000 mls	1 in 1000 or 0.1 p.c.	2 to 8 ms subcutaneously
Ammoniaæ Dil.	Strong solution of ammonia 333 mls., water <i>q.s</i> 1000 ml.	10 p.c. w/w	10 to 20 ms 0.6 to 1.2 ml.
Ammoniaæ Fortis		325 p.c. by weight	Used externally

Liquor	Composition	Strength	Dose
Ammonii	Strong solution of ammon acet 125	72 p c.	$\frac{1}{4}$ to 1 oz
Acetatis Dil	ml, water q s to 1000 ml.		8 to 30 ml
Ammonii	Acid acetic glacial 453 G, ammon.	575 p c.	15 to 60 ms
Acetatis	carb 330 G, liq ammon. fort 100		1 to 4 ml.
Fortis	ml or q.s., water q s to 1000 ml		
Arsenicalis	Arsenic trioxide 10 G, liq. pot	1 p c	2 to 8 ms
	hydrox 100 ml, acid hydrochlori		0.12 to 0.5 ml
	dil 28 ml. or q.s., water q.s. to		
	1000 mls		
Arseni et	Arsenic trioxide 1 G, red mercuric	1 p.c. of each	5 to 15 ms
Hydrargyri	iodide 1 G, water q.s. to 100 ml.		0.3 to 1 ml.
Iodidi			
Calciferols	Solution of calciferol in oil.	1 ml or 15 ms	5 to 10 ms
		contains 3000	or
		Units vita-	10 to 15 ms
		min D	
Calcii	Calcium hydroxide 1 G., water 100	0.15 p c	1 to 4 oz
Hydroxidi	ml		30 to 120 ml.
Cresolis	Cresol 500 ml, linseed oil 180 G, Pot.	50 p c.	Used
Saponatus	hydroxide 42 G., water q s. to 1000		externally
	mls		
Epispasticus	Cantharidin 4 gms, castor oil 25	0.4 p c.	Used
	mls., colophony 12 gms, acetone		externally
	q s to 1000 mls		
Ferri	An aqueous solution of FeCl ₃	15 p c ferric	5 to 15 ms,
Perchloridi	Obtained by oxidation of ferrous	chlori	0.3 to 1 ml
	chloride		
Formaldehydi	An aqueous solution	37 to 41 p c	
Glycerilis	Solution of glyceryl trinitrate in	$\frac{1}{100}$ gr in	$\frac{1}{2}$ to 2 ms
Trinitratis	alcohol	2 ms	0.03-0.12 ml
Hydrargyri	Mercuric chloride 1 gm., and water	$\frac{1}{100}$ gr in	30 to 60 ms
Perchloridi	q.s 1000 mls. by solution	60 ms.	2 to 4 mls
Hydrogenii	An aqueous solution of hydrogen	10 of oxygen	30 to 120 ms.
Peroxidi	peroxide	in l	2 to 8 mls.
Iodi Aquosus	Iodine 50 gm., potassium-iodide 100	5 p c. iodine	5 to 15 ms
	gm, distilled water q s 1000 ml.	10 p c pot.	0.3 to 1 mil.
		iodide	
Iodi Fortis	Iodine 10 G., pot. iodide 6 G, water	10 p.c iodine	Used
(Tr Iodi	10 ml, alcohol (90 p c) q.s to 100	6 p c pot.	externally
Fort.)	ml	iodide	
Iodi Mitis	Iodine 2 1/2 G, pot iodide 1 1/2 G.,	2.5 p c iodine	5 to 30 ms.
(Tr Iodi	water 2 1/2 ml, alcohol (90 p c) q s	1.5 p c pot.	0.3 to 2 ml
Mitis)	to 100 ml.	iodide	
Iodi Simplex	Iodine 9 G, alcohol (95 p c) q s to	$\frac{1}{2}$ gr. in	3 to 15 ms
	100 ml	15 ms.	0.2 to 1 ml
Magnesii	A solution of magnes. bicarbonate	2.5 p c.	1 to 2 ozs
Bicarbonatis	in water saturated with CO ₂		30 to 60
			mls
Morphinae	Morphine hydrochloride 1 gm, di-	$\frac{1}{4}$ gr in	5 to 30 ms
Hydro-	lute hydrochloric acid 2 mls,	30 ms or	0.3 to 2 ml
chloridi	alcohol (90 p.c.) 25 mls, and water	1 p c	
	q s to 100 mls		
Picis	Prepared coal tar 2 gms., quillaia	20 p c	Used
Carbonis	in powder 1 gm, and alcohol		externally
	(90 p.c) q s to 10 mls		
Plumbi	Strong lead subacetates solution 125	125 p c	Used
Subacetatis	mls, water q s. to 1000 mls.	liquor	externally
Dil.			
Plumbi	Lead acetate 250 gms., lead mon-	19 to 21.5 p c	Used
Subacetatis	oxide in powder 175 gms, and	lead	externally
Fortis	water q s to 1000 mls.		
Potassii	An aqueous solution containing 5		Used
Hydroxidi	p c of total alkali (KOH)		externally
Quininae	Quinine sulph 2 G, dilute sol. am-	$\frac{1}{2}$ gr in	30 to 60 ms.
Ammoniatas	mon. 10 ml, alcohol (60 p c) q s to	60 ms	2 to 4 ml
	100 ml		
Soda	Chlorinated lime, boric acid, sod	0.5 to 0.55 p c	Used
Chlorinatae	carb each q.s, water 1000 ml.	chlorine	externally
Chirurgicæ			
Sodi Chloridi	Sodium chloride 9 G, water q.s	0.9 p.c
Physiologicus	1000 ml		
Strychninae	Strychnine hydrochloride 1 gm.,	1 p c or $\frac{1}{10}$ gr	3 to 12 ms.
Hydro-	alcohol (90 p c) 25 mls, and	in 12 ms.	0.2 to 0.8 ml
chloridi	water q s to 100 mls.		

The following liquors are all 1 p.c., i.e. contain 1 gr. in 110 ms. — Liquor arsenicalis, arseni et hydrarg. iodidi, glyceryli trinitatis, morphinæ hydrochlor., strychninæ hydrochlor.

The following liquors are meant for external use only:—

Liquor ammoniæ fort., Liq. cresolis saponatus, Liq. epispasticus. Liq. formaldehydi, Liq. iodi fort., Liq. picis carbonis, Liq. plumbi subacetatis fort. and dilutus, Liq. potassii hydroxidi, and Liq. sodæ chlorinatæ chirurgicæ.

Lotiones.—Lotions are solutions or mixtures of active ingredients for external application only. There is only one.

Lotio	Composition	Strength	Action and uses
Hydrargyri Nigra	Mercurous chloride 7 gms, glycerin 50 mls., solution of cal hydroxide q.s. to 1000 mls.	07 p c.	A stimulating alterative application to syphilitic sores

Mella.—**Mellita.** Honeys are liquid preparations containing honey as a vehicle. They are three in number.

Mel Depuratum is honey melted and strained through flannel.

Mel	Preparation	Strength	Dose	Action
Boracis	Borax 10 gms, purified honey 85 gms. and glycerin 5 gms	10 p c.	Used locally	An alternative to diseased mucous surface
Oxymel	Acetic Acid 15, water 15, honey q s. to 100 ml	sp gr 1.258 to 1.263	30 to 120 ms (2 to 8 mls)	Expectorant
Oxymel Scillæ	Squill 5 G, acetic acid 9 ml., water 25 ml, honey q s	5 p c squill	30 to 60 ms. (2 to 4 mls.)	Used as a vehicle Expectorant

Misturæ—Mixtures are preparations in which drugs are simply dissolved in water or suspended in it. The official mixtures are only two in number.

Mistura	Preparation	Strength	Dose
Magnesi Hydroxidi (Cream of Magnesia)	Mag. sulph. 47.5 G, sodium hydroxide 15 G, light mag oxide 52.5 G, water q s. 1000 ml	12½ gr in 240 ms.	60 to 240 ms. 4 to 16 mls.
Sennæ Composita	Magnesium sulphate 25 gms, liquid extract of liquorice 5 mls, tinct. card Co. 10 mls., spt ammon aromat. 5 mls, and flesh infusion of senna q s to 100 mls	120 grs in 1 oz oi 25 p c mag sulph	1 to 2 ozs 30 to 60 mls.

Mucilagines—Mucilages are solutions of gummy substances in water. They are two in number.

Mucilago	Ingredients	Dose
Acaciæ	Acacia 40 G, chloroform water 60 ml	60 to 240 ms 4 to 16 mls.
Tragacanthæ	Tragacanth 12.5 G, alcohol (90 p.c) 25 ml, chloroform water q.s to 1000 mls.	60 to 240 ms. 4 to 16 mls.

Oculenta. Eye ointments are preparations meant for application to the eye. They are prepared as follows:—

Melt together 90 parts by weight of yellow soft paraffin and 10 parts by weight of wool fat, filter while hot and sterilise by heat at 150°C. for one hour. The drug required for 100 grms. is mixed in a sterile mortar and the melted basis added to weigh 100 grms.

Oculentum	Ingredients	Strength
Atropinæ	Atropine sulph	0.25 p.c.
Atropinæ c	Atropine sulphate, yellow mercuric oxide	0.125 p.c.
Hydrargyri Oxido		1 p.c.
Cocainæ	Cocaine hydrochloride	0.25 p.c.
Hydrargyri Oxidi	Yellow mercuric oxide	1 p.c.
Hyoscine	Hyoscine hydrobromide	0.125 p.c.
Iodoformi	Iodoform	4 p.c.
Phyosostigminæ	Phyosostigmine salicylate	0.125 p.c.

Oleata.—Oleates are preparations of bases with oleic acid, having a solid or semi-solid consistence. Only one preparation, viz:—

Hydrargyrum Oleatum.—Yellow mercuric oxide 20 grms., liquid paraffin 5 grms., oleic acid 75 grms.

Olea. Oils.—There are thirty one oils in the B.P. They can be grouped under three classes—fixed, volatile, and compound; the former being obtained by expression, and the volatile by distillation, except in the case of lemon oil which is a volatile oil though obtained by expression. Oil of cade is obtained by dry or destructive distillation.

Of the ten fixed oils, cod-liver oil is an animal product, and the rest are expressed at ordinary temperatures. Oil of theobroma is solid in cold weather and semi-solid or fluid in hot weather. The colour of cajuput is deep-green and that of cade is almost black. Oil of turpentine is almost colourless. The rest display various shades of straw, yellow and pale-brown.

FIXED OR EXPRESSED OILS

Oleum	Source	Dose	Action
Amygdalæ	Bitter or sweet almonds	½ to 1 oz	Demulcent, emollient
Arachis	Seeds	½ to 1 oz	Emollient
Gossypii	Seeds	½ to 1 oz	Emollient and demulcent
Seminis			
Hydnocarp	Seeds. By cold expression	5 to 15 ms up to 60 ms	In leprosy
Lin	Linseed	½ to 1 oz	Demulcent and emollient
Morrhue	Expressed from the fresh liver of Cod	15 to 30 ms or 45 to 90 ms	Nutritive, tonic and alterative
Olivæ	Ripe fruit	½ to 1 oz	Emollient
Ricini	Fresh seeds	60 to 240 ms	Cathartic
Sesami	Seeds	½ to 1 oz	Emollient
Theobromatis	Expressed from roasted seeds	Used externally	For making suppositories

VOLATILE, ESSENTIAL, OR DISTILLED OILS

Oleum	Source	Dose	Action
Abietis	Fresh leaves		Rubefacient
Anethi	Dill fruit	1 to 3 ms	Carminative
Anisi	Anise or star-anise	1 to 3 ms	Do

Oleum	Source	Dose	Action
Cadinum	Woody portions, by destructive distillation	Used externally	Astringent
Cajuputi	Fresh leaves	1 to 3 ms	Antispasmodic
Cari	Caraway fruit	1 to 3 ms	Carminative, antispasmodic
Caryophylli	Cloves	1 to 3 ms	Do
Chenopodii	Fresh plants	3 to 15 ms	Anthelmintic
Cinnamomi	Cinnamon	1 to 3 ms.	Antispasmodic
Coriandri	Coriander fruit	1 to 3 ms	Do
Eucalypti	Fresh leaves	1 to 3 ms	Antiseptic
Hydnocarpus	Esterifying fatty acids of hydnocarpus oil with ethyl alcohol and subsequent distillation	5 to 15 ms increasing to 60 ms	In leprosy
Lavandulæ	Fresh flowering tops	1 to 3 ms.	Antispasmodic
Limonis	Fresh lemon peel by expression	1 to 3 ms	Aromatic
Menthæ	Fresh flowering tops	1 to 3 ms	Antispasmodic and carminative
Piperitæ			Carminative and narcotic
Myristicæ	Nutmeg	1 to 3 ms.	Rubefacient
Rosmarini	Flowering plant	1 to 3 ms.	Urinary antiseptic
Santal	Wood of <i>Santalum album</i>	5 to 15 ms	Do
Santal	Wood of <i>Eucarya spicata</i>	5 to 15 ms.	
Australiensis			
Terebinthinæ	From oleo-resin, turpentine	3 to 10 ms or 120 to 240 ms As anthelmintic	Rubefacient, diuretic, and anthelmintic

Oleum Iodisatum is an iodine addition product of poppy seed oil, and is prepared by treating poppy seed oil with hydriodic acid.

The dose of most of the volatile oils is from 1 to 3 ms. or 0.06 to 0.2 mil, with the exception of sandal wood, 5 to 15 ms, chenopodium, 3 to 15 ms., and turpentine, 3 to 10 ms.

Volatile oils are combined with many B.P. pills, either for their carminative effect or because of their smell to serve as a means of distinction between various pill masses of similar appearance.

Pasta. Pastes are prepared like ointments and intended for external application. They are usually spread on lint and covered with a layer of cotton wool and kept in position by bandage, or adhesive plaster.

Pasta Zinci Oxidi Co.—Zinc oxide, starch, each 250 grms., white soft paraffin 500 grms.

Pilulæ.—Pills are solid or semi-solid globular masses containing medicinal agents intended to be swallowed whole without chewing. Pills are always popular for easy administration, being portable, easily swallowed and containing a definite and correct dose. They should not be too hard unless intended to dissolve slowly, or so soft as to lose shape and stick together. To prevent this and to cover the nauseous taste they are coated or gilded. In India and tropical countries, pills get too hard or too soft according to the variations of the weather; being liable to become soft and to run together during the rains. To avoid this, they should be kept in well stoppered bottles. Pills, as a rule, should not weigh more than 5 grains each. A mass of the consistence of firm clay is first made by pounding and kneading the drugs together in a mortar; and subsequently this mass is either rolled and divided by a pill-making machine, or when the quantity is small, the same process is done over a pill-tille by the spatula. The pills should be perfectly round and firm. An excipient is always necessary to make a pill-mass.

The B.P. pills are seven in number.

Pilula	Composition	Strength	Action
Aloes	Aloes 58 gms, hard soap 29 gms, oil of caraway 3 mls, syr of glucose 10 gms or q.s.	58 p c	Cathartic
Aloes et Asafœtidæ	Aloes, asafetida, hard soap each 3 gms, syr of glucose 1 gm or q.s.	30 p c	Cathartic and antispasmodic
Aloes et Ferri	Exsiccated ferrous sulph 10 G, aloes 20 G, cinnamon, cardamom, ginger, each 12 G, syrup of glucose 34 G or q.s	$\frac{1}{2}$ gr ferrous sulph or $\frac{1}{4}$ gr. iron in 8 gr 12 5 p.c	Cathartic and emmenagogue
Colocynthis et Hyoscyami	Colocynth 125 G, aloes 25 G, scammony resin 25 G, oil of clove 4 ml., curd soap 7 G, ext Hyosc. sic 12 5 G, syrup of glucose 14 G or q.s.		Cathartic
Ferri Carbonatis	Exsiccated ferrous sulphate 34 gms, exsiccated sodium carbonate 216 gms. acacia 84 gms, tragacanth 2 gms, liquid glucose 32 gms, and water 2 mls	20 p c (Ferrous Carb)	Tonic and emmenagogue
Hydrargyri	Mercury 33 G, syrup 14 G, liquid glucose 15 G, glycerin 5 G, liquorice 33 G	33 p.c	Alterative and laxative
Rhei Co.	Rhubarb 25, powder aloes 20, myrrh 14, hard soap 14, oil of peppermint 2, syrup of glucose 25, or q.s	25 p c	Stomachic, tonic, and a gentle cathartic

All the cathartic pills in the above table contain aloes except the mercurial pill. All pills are given in 4 to 8 grain doses, except Pil. Ferri Carbonatis, 5 to 30 grs.

The colour of the B.P. pill-masses is blackish-brown or black, with the exception of Pil. Hydrargyri, which is blue. Many of the pills can be recognised by their smell, for instance, Pil. Rhei Co. by the smell of peppermint; and Pil. Aloes et Asafœtidæ by that of asafetida

Pulverata. Powders of crude drugs intended for internal use. They are single vegetable drugs reduced to a fine powder, assayed and adjusted to contain a definite percentage of active ingredients by addition of lactose, the object being to maintain a uniform percentage of active principles. They are six in number.

Pulverata	Ingredients	Strength	Dose
Belladonna	Leaf. Contains 0.3 p c hyoscyamine	$\frac{1}{100}$ gr alkaloids in 3 grs	$\frac{1}{2}$ to 3 grs 0.08 to 0.2 gm
Digitalis	Leaf reduced to coarse powder, adjusted to contain 10 Units in 1 G	6 Units in 10 grs	$\frac{1}{2}$ to $1\frac{1}{2}$ grs. or 3 to 10 grs single dose
Ipecacuanha	Ipecacuanha reduced to a fine powder; contains 2 p c of emetine	$\frac{1}{25}$ gr in 2 grs.	$\frac{1}{2}$ to 2 grs or 15 to 30 grs single dose
Jalapa	Jalap reduced to fine powder	10 p.c resin	5 to 20 grs 0.3 to 1.2 gms.
Nux Vomica	Nux vomica 12 p c strychnine	$\frac{1}{20}$ gr in 4 grs.	1 to 4 grs. 0.06 to 0.25 G.
Opium	Opium Adjusted to contain 10 p c morphine	$\frac{3}{10}$ gr in 3 grs.	$\frac{1}{2}$ to 3 grs 0.03 to 0.2 G

Pulveres.—Powders are mixtures of dry substances reduced to a fine powder and intimately mixed together. Powders should be

mixed in a very clean mortar (a glass one being the best). The method of mixing greatly affects the miscibility of powders.

The B.P. powders are eight in number.

Pulvis	Composition	Strength	Dose	Action
Cretæ Aromaticus	Chalk 25, cinnamon 10, nutmeg 8, clove 4, cardamom 3, sucrose 50	25 p.c.	10 to 60 grs 0.6 to 4 G.	Aromatic, astringent, and antacid
Cretæ Aromaticum Opio Effervescens Co	Aromatic chalk powder 975, opium 25	25 p.c. (opium)	10 to 60 grs. 0.6 to 4 G.	Aromatic, astringent
	Sodium potassium tartarate 75, sodium bicarbonate 25, mix, and wrap in blue paper, tartaric acid in dry powder 25, wrap in white paper.	116, 38 1/2 & 38 1/2 grs	193 grs 12.5 G	Hydragogue cathartic
Glycyrrhizæ Co.	Senna leaf 16, liquorice 16, fennel 8, sublimed sulphur 8, sucrose 52.	16 p.c. Senna	60 to 120 grs 4 to 8 G	A mild cathartic
Ipecac. et Opi	Ipecac. powder 1, opium powder 1, lactose 8	10 p.c. (opium)	5 to 10 grs. 0.3 to 0.6 G	Diaphoretic, anodyne
Jalapæ Co.	Jalap 3, acid potassium tartarate 6, ginger 1	30 p.c. Jalap	10 to 60 grs. 0.6 to 4 G	Hydragogue purgative
Rhei Co.	Rhubarb 25, light and heavy magnesium carbonate, each 32 1/2 and ginger 10	25 p.c. rhubarb	10 to 60 grs. 0.6 to 4 G	Antacid, stomachic, cathartic
Tragacanthæ Co.	Tragacanth 15, acacia 20, starch 20, and sucrose 45	15 p.c.	10 to 60 grs. 0.6 to 4 G.	Demulcent

Pulvis Vitamin B, is prepared from rice polishings, yeast, wheat embryo or other suitable materials; dried and finally adjusted with fuller's earth to contain 100 Units in 1 gm. 1 gm. contains 100 Units of antineuritic vitamin. *Dose*.—15 to 30 grs. or 30 to 90 grs.

Sera are preparations from serum, containing antitoxic globulins or immune substances having a specific power of neutralising the toxins of the particular organisms against which they have been prepared. There are nine in the B.P.

Serum	Preparation	Dose
Antidysentericum (Shiga)	Contains the immune substances having specific therapeutic value in <i>B. dysenteriae</i> (Shiga)	4000 to 10,000 Units by injection
Antipneumococcicum I	Contains the immune substances having a specific action in diseases due to <i>D. pneumoniae</i> Type I.	50,000 to 150,000 Units by intravenous injection
Antipneumococcicum II	Prepared in the same way as Type I	Same as Type I.
Antitoxinum Diphthericum	Contains the antitoxin globulins having specific power of neutralising the toxin formed by <i>Corynebacterium diphtherie</i> .	500 to 1000 Units as prophylactic, 10,000 to 20,000 Units as curative
Antitoxinum Oedematiens	Contains the antitoxin globulins having specific power in neutralising the toxin of <i>Cl. oedematiens</i>	20,000 Units as prophylactic; 50,000 to 100,000 Units as curative
Antitoxinum Staphylococcicum	Contains the antitoxin globulins having specific power in neutralising the toxins of certain strains of <i>Staphylococcus</i>	5000 to 20,000 Units.

Serum	Preparation	Dose
Antitoxinum Tetanicum	Contains the antitoxic globulins having specific power of neutralising the toxin formed by <i>B tetani</i>	1000 to 2000 Units (prophylactic), 20,000 to 40,000 Units (therapeutic)
Antitoxinum Vibriosepticum	Contains the antitoxin globulins having specific power of neutralising toxin formed by <i>C vibrio septique</i>	5000 Units as prophylactic, 10,000 to 20,000 Units as curative
Antitoxinum Welchicum	Contains the antitoxin globulins having specific power of neutralising the toxin of <i>B perfringens</i>	4000 Units (prophylactic), 10,000 to 20,000 Units (therapeutic) intravenously

Spiritus. Spirits.—The B.P. spirits, with the exception of Industrial Methylated Spirit, are alcoholic solutions of volatile oils and ethers. They can be divided into two classes—**simple** and **compound**. The simple spirits are solutions of essential oils, ether and chloroform in alcohol (90 p.c.), which often get turbid when diluted with water. The compound spirits contain more than one ingredient. The B.P. spirits are seven in number, of which five are simple and two compound. The dose of all simple spirits is 5 to 30 ms., or 0.3 to 2 mils, except Spirit. Ætheris, 15 to 60 ms. or 1 to 4 mils.

SIMPLE SPIRITS

Spiritus	Composition	Strength	Action
Ætheris	Ether and alcohol (90 p.c.)	33 p.c.	A diffusible stimulant, antispasmodic and carminative
Cajuputi	Oil of cajuput and alcohol (90 p.c.)	10 p.c.	Carminative and antispasmodic
Camphoræ	Camphor and alcohol (90 p.c.)	10 p.c.	Stimulant and antispasmodic
Chloroformi	Chloroform and alcohol (90 p.c.)	5 p.c.	A diffusible stimulant and antispasmodic
Menthæ Pip.	Oil of peppermint and alcohol (90 p.c.)	10 p.c.	Carminative and antispasmodic

COMPOUND SPIRITS

Spiritus	Composition	Strength	Dose	Action
Ætheris Nitrosi	Nitric acid, sulphuric acid, copper and alcohol (90 p.c.). By distillation	1.25 to 2.5 p.c ethyl nitrite	15 to 60 ms 1 to 4 mils	Diaphoretic, diuretic, antispasmodic
Ammonia Aromaticus	Carbonate of ammonia 25 gms., strong solution of ammonia 50 mils, oil of nutmeg 3 mils, oil of lemon 5 mils, alcohol (90 p.c.) 750 mils, and distilled water q.s 1000 mils	2.1 to 2.4 p.c ammonia 1.265 to 1.435 p.c CO ₂	15 to 60 ms 1 to 4 mils	Cardiac stimulant, antispasmodic and carminative

Suppositoria.—**Suppositories** are solid conical-shaped masses containing some active ingredients, for rectal medication. With the exception of the glycerin suppository, all of them are blended with oil of theobroma which melts at 25°C. The melting point may be raised to 37°C. by the addition of white beeswax. They consequently dissolve slowly when introduced into the rectum. They weigh

about 15 grains (1 gramme) each, and are made in conical moulds of massive gun-metal. They are seven in number.

Suppositorium	Composition	Strength in each	Action
Acidi Tannici	Tannic acid	3 grs or 0.2 G	A local astringent and styptic
Belladonnæ	Liquid extract of belladonna 2½ ms	¼ gr (alkaloids)	A local anodyne
Glycerini	Gelatin 14 gms, glycerin 70 gms, and distilled water q s	70 p c (by weight)	Laxative
Iodoformi	Iodoform	3 grs	A local antiseptic
Morphinæ	Morphine hydrochloride	¼ gr	A local anodyne
Phenolis	Phenol	1 gr or 0.06 G	Antiseptic and a local anæsthetic
Plumbi c. Opio	Lead acetate and opium	3 grs and 1 gr	Anodyne and astringent

Suppositories are used either to produce a local action on the rectum, or on the adjacent pelvic organs such as the uterus and the bladder, or to produce their general effect on the system after absorption. Thus morphine suppository may be used either to soothe pain and irritation in the rectum or pelvic organs, or to induce sleep.

Syrupi.—Syrups are fluid preparations of drugs containing a sufficient quantity of sucrose, either to preserve them to or make their administration more agreeable. The dose of all syrups is from 30 to 120 ms, except that of squill and Easton's syrup which are given in 30 to 60 ms. They are twelve in number. If the concentration of sucrose is less than that in simple syrup, the syrup may undergo fermentation unless some preservative is added.

Syrupus	Composition	Strength	Action
Syrupus	Sucrose 667 G., water q s to 1000 G		A sweetening agent
Aurantii	Tincture of orange 125 mls, syrup q s to 1000 mls	125 p c	A flavouring agent
Ferri Iodidi	Iron 19 G., iodine 58 G., acid hypophos dil 10 ml, water q s., syrup q s to 1000 ml	5 p c ferrous iodide	Hæmatinic tonic
Ferri Phosphatis Co	Iron 4.3 G., phosphoric acid 48 ml., calcium carb 18.6 G., potassium bicarb 1 G., sod phosph 1 G., cochineal 3.5 G., sucrose 700 G., orange-flower water 50 ml, water q s to 1000 ml.	0.9 p c ferrous phosph 1.4 p c tricalcium phosph	Do
Ferri phosph. c Quin et Strychnina	Iron 8.6 G., phosphoric acid 40 ml., strychnine hyd 0.3 G., quinine sulph. 1.48 G., syrup 560 ml, glycerin 140 ml, water q s to 1000 ml	1 gr ferrous phosphate, ¼ gr of Quin sulph and 1/100 gr of strychnine in 1 dr	A general and nerve tonic. Hæmatinic
Glucosi Liq	Glucose liquid 333 G., syrup 667 G.	83 p c	An excipient for pills
Limonis	Lemon peel 60 G., alcohol (60 p c), q s, citric acid 24 G., syrup q s to 1000 ml.	6 p c	A flavouring agent
Pruni Serotinæ	Wild cherry bark 15 G., sucrose 80 G., glycerin 5 ml, water q s to 100 ml	15 p c	A sweetening agent
Scillæ	Vinegar of squill 45 mls, sucrose 80 gms, water q s. to 100 mls	45 p c squill	Expectorant and emetic
Sennæ	Liquid extr of senna 250 ml, oil of coriander 15 ml, sucrose 700 G., water q s to 1000 ml	25 p.c.	A mild cathartic

Syrupus	Composition	Strength	Action
Tolutanus	Balsam of tolu 25 gms, sucrose 660 gms, and water q s to 1000 gms.	25 p c	A sweetening agent for cough mixtures
Zingiberis	Strong tincture of ginger 5 ml., syrup q s to 100 ml	5 p c	Calminative and antispasmodic

Tabellæ. Tablets —According to the B.P. tablets are small flat pieces of chocolate containing minute doses of medicinal agents. Tablet preparations are very popular now, but are often useless, since when made by compression, they may become so hard and insoluble as to be recovered quite undissolved from the faeces. According to their mode of preparation, they may be divided into three classes, viz:—(1) those made by compression; (2) those made without compression but by moulding, commonly known as tablet-triturates; and (3) those prepared from a chocolate basis, as ordered by the B.P.

There is only one tablet in the B.P.

Tabella Glycerylis Trinitratis.—Made of chocolate, each weighing 5 grains (0.3 gm.) and containing $1\frac{1}{8}$ gr. (0.0005 G.) of glyceryl trinitrate. *Dose*—1 or 2 tablets

Tincturæ.—Tinctures are alcoholic solutions containing all the active ingredients of the drugs of which they are compounded. In this respect they differ from the official spirits which are merely alcoholic solutions of essential oils. They are prepared either by (a) *maceration*, (b) *percolation*, or (c) *simple solution*. They are thirty-three in number; of these, only one is from the animal kingdom, viz.:—Tr. Cocci.

Alcohol of various strengths is used to make tinctures, such as alcohol (90 p.c.), alcohol (70 p.c.), alcohol (60 p.c.) and alcohol (45 p.c.) One tincture is made with ether, viz., Tr. Lobeliæ Ætherea.

The total bulk for all tinctures is 1000 mls with alcohol, or with alcohol and water. The quantities given are for 1000 mls.

Some preparations which were formerly grouped under tinctures are now known as Liquors, being simple solutions of chemical substances. They are liquor iodi fortis and mitis, liquor quiniæ ammoniata, liquor ferri perchlor.

Twenty-four tinctures are "Simple" having only one ingredient and one solvent. Five tinctures are called "Compound," having more than one ingredient. Another group of four tinctures are not called compound in the B.P. though they contain more than one ingredient and a solvent. They may be named "Complex"

We shall group tinctures under three heads, viz.:—(1) Simple, (2) Compound, and (3) Complex.

SIMPLE TINCTURES

Tinctura	Ingredients	Alcohol p c in Menstruum	Process	Strength	Dose
Asafetida	Asafetida 200 G.	70	M	20 p c.	30 to 60 ms.
Aurantii	Fresh bitter peel 250 G.	90	M	25 p c	30 to 60 ms.
Belladonnæ	Belladonna leaf 100 G.	70	P	0.03 p c alkaloids	5 to 30 ms.

Tinctura	Ingredients	Alcohol p c in Menstruum	Process	Strength	Dose
Calumbæ	Calumba 100 G	60	M	10 p c	30 to 60 ms.
Capsici	Capsicum 50 G	60	M	5 p c	5 to 15 ms
Cinchonæ	Extract of Cinchona 100 G	70	S	1 p c alkaloids	30 to 60 ms
Cocci	Cochineal 100 G	45	M	10 p c	5 to 15 ms.
Colchici	Liquid extract 100 ml	60	S	0.03 p c colchicine	5 to 15 ms.
Digitalis	Leaf 80 G, or powdered leaf containing 1000 Units.	70	P	6 Units in 90 ms.	5 to 15 ms. or 30 to 90 ms
Hyoscyami	Liquid extract 100 ml	70	S.	0.005 p c alkaloids	30 to 60 ms.
Krameriæ	Krameria 200 G	60	P.	20 p c	30 to 60 ms
Limonis	Lemon peel 250 G	60	M	25 p c.	30 to 60 ms
Lobeliæ	Lobelia 200 G, spt ether q s. to 1000 ml	—	P	20 p c.	5 to 15 ms.
Ætherea	Myrrh 200 G	90	M	20 p c	30 to 60 ms.
Myrrhæ	Liquid ext 83 4 ml, alcohol 500 ml, water to 1000 ml.	90	S	0.125 p c.	10 to 30 ms
Nucis	Opium 200 G, alcohol q s, water q s to 1000 ml	90	S	strychnine 1 p.c.	5 to 30 ms
Vomice	Quassia 100 G	45	M	morphine 10 p c.	30 to 60 ms.
Opii	Quillaia 50 G	45	P	5 p c.	30 to 60 ms.
Quassia	Squill 100 G	60	M	10 p c	5 to 30 ms
Quillaia	Liquid extract 200 ml	60	S	20 p.c.	30 to 60 ms.
Scilla	Liquid extract 100 ml	45	S	0.025 p c alkaloids	5 to 30 ms.
Senegæ	Strophanthus 100 G, alcohol 500 ml. or q s	70	P		2 to 5 ms.
Stramonii	Balsam of tolu 100 G	90	S.	10 p c	30 to 60 ms.
Strophanthi	Ginger 500 G	90	P	50 p c	5 to 10 ms.
Tolutana	Strong tincture of ginger 200 ml	90	S	30 to 60 ms.
Zingiberis					
Fortis					
Zingiberis					
Mitis					

COMPOUND TINCTURES

Tinctura	Ingredients	Alcohol p c in Menstruum	Process	Strength	Dose
Benzoini Co	Benzoin 100 gms, storax 75 gms, tolu 25 gms., aloes 20 gms	90	M.	10 p.c	30 to 60 ms. 2 to 4 mils
Cardamomi Co	Cardamom 14 gms, caraway 14 gms, cinnamon 28 gms, cochineal 7 gms, glycerin 50 mils.	60	P	14 p c.	30 to 60 ms. 2 to 4 mils
Cinchonæ Co.	Ext of cinchona 50 gms, bitter orange peel 50 gms, cochi- neal 3 gms, serpentry 25 gms	70	P	1/4 gr alkaloids in 60 ms	30 to 60 ms 2 to 4 mils
Gentianæ Co.	Gentian 100 gms., bitter orange peel 37 1/2 gms, cardamom seeds 12 1/2 gms	45	M.	10 p c.	30 to 60 ms 2 to 4 mils,
Rhei Co.	Rhubarb 100 gms, cardamom, coriander, each 12 5 gms, glycerin 100 mils.	60	P	10 p.c	30 to 60 ms 2 to 4 mils

COMPLEX TINCTURES

Tinctura	Ingredients	Alcohol p c in Menstruum	Process	Strength	Dose
Catechu	Catechu 200 G, cinnamon 50 G, alcohol q s to 1000 mls	45	M.	20 p c.	30 to 60 ms. 2 to 4 mls.
Ipecacu- anhæ	Liquid extract 50 ml, alcohol 200 ml, dilute acetic acid 165 mls, glycerin 200 ml, water to 1000 ml	90	S.	01 p c alkaloids	10 to 30 ms or $\frac{1}{2}$ to 1 oz emetic
Opii Campho- rata (Tr. Campho- ræ Co.)	Tr. opii 50 ml, benzoic acid 5 G, camphor 3 G, oil of anise 3 ml, alcohol q s 1000 ml	60	S.	005 p c morphine or $\frac{1}{17}$ gr in 60 ms	30 to 60 ms 2 to 4 mls.
Valerianæ Ammono- niata	Valerian powder 200 G, oil of nutmeg 3 mls, oil of lemon 2 mls, dilute ammonia solution 100 mls, alcohol 900 mls	60	M	20 p c.	30 to 60 ms. 2 to 4 mls.

The following tinctures are standardised:—

Tr. belladonnæ, cinchonæ, cinchonæ co, colchici, hyoscyami, ipecacuanhæ, nucis vomicæ, opii, opii camphorata, and stramonii are standardised by chemical assay.

Tinctures of digitalis and strophanthus are standardised by biological assay.

The dose of most Tinctures is from 30 to 60 ms., except

Ipecacuanha and nux vomica, 10 to 30 ms.

Belladonna, opium, squill and stramonium, 5 to 30 ms.

Capsicum, cochineal, digitalis and lobelia 5 to 15 ms.

Ginger (strong) 5 to 10 ms.

Strophanthus 2 to 5 ms.

The dose of tincture of digitalis when given in a single dose is 30 to 90 ms.

Toxins are three in number.

Toxinum	Preparation	Dose
Diphthericum Calefactum (Schick Control)	Schick test toxin heated to a temperature not less than 70° for not less than 5 minutes	3 ms by intradermal injection.
Diphthericum Detoxicatum	A sterile filtrate from a culture on nutrient broth of <i>Corynebacterium diphtheriæ</i> .	By subcutaneous injection the volume indicated on the label as the dose, on 2 or 3 occasions, at intervals of 2 to 4 weeks
Diphthericum Diagnosticum (Schick Test Toxin)	Prepared from a culture on nutrient broth of <i>Corynebacterium diphtheriæ</i>	3 ms by intradermal injection

Trochisci.—Troches or Lozenges are flat solid tablets composed of a basis and one or more active drugs uniformly divided, for the purpose of slowly melting in the mouth. The quantities given are for 1000 lozenges. The B.P. has the following for the preparation of their bases:—

Take 1000 times the quantity of the drug ordered for one lozenge; dissolve such salts of alkaloids as may be ordered in 20 mls, or a sufficient quantity of distilled water; mix the solution with 1000 gms.

Note—M=Maceration. P=Percolation. S=Solution.

of sucrose and 70 grms. of acacia, both finely powdered. Incorporate 20 mils. of tincture of tolu, and any other drugs ordered. Make into a paste with sufficient distilled water; divide into 1000 equal lozenges, dry at a moderate temperature.

Trochiscus	Ingredients	Strength in each	Action and uses
Acidi Tannici Bismuthi Comp	Tannic acid 30 G Bismuth carb 150 G, heavy magnes carb 150 G, cal carb 300 G, acacia 70 G, sucrose 1000 G, oil of rose 0.05 ml, water q s	$\frac{1}{2}$ gr $2\frac{1}{4}$ gr $2\frac{1}{4}$ gr $4\frac{1}{2}$ gr.	A local astringent Antacid
Krameria et Cocainæ Morphina et Ipecacuanhæ Phenolis	Extract of Krameria 60 G Extract krameria 60 G cocaine hydrochloride 3 G Morphine hydr 2 G, powdered ipecac 6 G Liquefied phenol 35.5 mls, acacia 90 G, tragacanth 30 G, citric acid 7 G, camphor 3 G, sucrose 1000 G, water q s	1 gr 1 gr $\frac{1}{50}$ gr $\frac{1}{32}$ gr $\frac{1}{10}$ gr $\frac{1}{2}$ gr.	Astringent Astringent and anæsthetic Allays cough Antiseptic

Unguenta.—Ointments are semisolid or soft preparations for external application containing some active drugs mixed with a fatty, oily or paraffin basis. Lard, either plain or benzoinated, glycerin, prepared suet, beeswax, etc., either alone or in combination, form the basis of all B.P. ointments.

There are nineteen ointments in the B.P. They may be divided into two classes, viz.—(1) General, and (2) Mercurial.

GENERAL OINTMENTS

Unguentum	Composition	Strength	Action and uses
Acidi Borici	Boric acid 1, white paraffin ointment 9	10 p c.	Antiseptic
Acidi Salicylici	Salicylic acid 2, white paraffin ointment 98	2 p c.	Antiseptic
Acidi Tannici	Tannic acid 20, glycerin 20, yellow beeswax 12, benzoinated lard 48	20 p c.	Astringent
Aquosum	Water 240 ml, borax 10 G, white beeswax 125 G, white soft paraffin 125 G, olive oil 500 ml	24 p c	Antiseptic, emollient
Capsici	Capsicum 25 G, hard paraffin 10 G, yellow soft paraffin 75 G, lard 10 G	25 p.c.	Rubefacient
Chrysarobini	Chrysarobin 4, simple ointment 96	4 p c.	Antiparasitic and stimulant application for psoriasis
Paraffini	White beeswax 20 G, hard paraffin 80 G, white or yellow soft paraffin 900 G	.	A basis for ointment (demulcent)
Phenolis	Phenol 30, white beeswax 75, lard 50, hard paraffin 75, white soft paraffin 770	3 p c	Antiseptic
Simplex	Wool fat 50, hard paraffin 100, white or yellow soft paraffin 850		Basis for ointment
Sulphuris	Sublimed sulphur 1, simple ointment 9	10 p.c.	Antiparasitic Cures scabies
Zinci Oleatis	Zinc sulphate 30 G, hard soap shavings 90 G, boiling water and white soft paraffin, of each q s	50 p c. oleate	A mild astringent for eczema
Zinci Oxidi	Zinc oxide 15, simple ointment 85.	15 p c.	Mild astringent

MERCURIAL OINTMENTS

Unguentum	Composition	Strength	Action and uses
Hydrargyri	Mercury 30, benzoinated lard 65, suet 5	30 p c	Resolvent, anti-parasitic
Hydrargyri Ammoniati	Ammoniated mercury 50, simple ointment 950	5 p c	Antiparasitic
Hydrargyri Comp	Mercury ointment 40, yellow beeswax, olive oil, each 24, camphor 12	12 p c of mercury	Destroys pediculi
Hydrargyri Nitratis Dilutum	Mercuric nitrate ointment 2, yellow soft paraffin 8	20 p c. Ung.	Absorbent, useful in glandular enlargement, etc
Hydrargyri Nitratis Forte	Mercury 1 gm, nitric acid 3 mls, lard 4 gms, olive oil 7 gms	Hyd Nit 67 p c of mercury	Same as above
Hydrargyri Oleati	Mercuric oleate 25, simple ointment 75	25 p c	Invaluable in eczema, tinea tarsi
Hydrargyri Subchloridi	Mercurious chloride 20, simple ointment 80	20 p c	A local alterative, astringent and stimulant.
			Same as Ung Hydrarg
			Antisyphilitic, alterative and resolvent

Vaccina. Vaccines. Three in number.

Vaccinum	Preparation	Dose
Tuberculinum Pristinum	The concentrated filtrate from a fluid medium on which <i>B tuberculosis</i> has been grown	$\frac{1}{50}$ to $\frac{1}{12}$ minim (diagnostic), $\frac{1}{50000}$ min gradually increased (by subcutaneous injection)
Typho-paratyphosum	Sterile suspension of <i>B typhosus</i> , <i>B paratyphosus A & B</i> which have been killed by heat	1st dose 0.5 ml. 2nd dose 1.0 ml after 7 to 10 days subcutaneously
Vaccinæ	A preparation of the substance obtained from the vesicles produced by inoculation of vaccinia virus on the skin of healthy animals	1 minim by scarification

NON-OFFICIAL OR NON-PHARMACOPŒIAL PREPARATIONS

Ampoulæ or ampoules are glass containers intended for injection.

Balnea. Baths.—The immersion of the whole or a part of the body in some liquid or vapour is called a bath. It is said to be general when the whole body is brought under its influence, and local when a part only

Properly speaking, only medicated baths come under non-official preparations; but a description of the different kinds of medicated and non-medicated baths will be given here.

A. Cold Bath.—Temperature 35° to 70° F. Average 50° to 60° F. It has a powerful tonic action, increasing digestion, metabolism and body weight; but in order to obtain these effects the bath should not be continued long after the primary reaction has set in. If it is prolonged it may cause secondary depression followed by delayed reaction. In fevers, it abstracts heat and thereby lessens tissue change and prevents complications; hence it is very useful in hyperpyrexia of rheumatism, typhus, typhoid, and remittent fevers, and pneumonia. The bath must be repeated if the temperature rises. There are several ways of using a cold bath. The following are a few examples —

1. Cold Affusion.—In this 5 to 6 gallons of cold water are thrown

over the body. It is valuable for resuscitating persons from syncope, narcotic poisoning, convulsions, sunstroke, hysteria, etc.

2. **River Bath.**—Bathing in the river is more invigorating than a full cold bath either in a tub, reservoir, or a tank. It stimulates digestion, gives tone to the system and strengthens muscles, especially if it is accompanied by swimming, or if the current of the water is very strong.

3. **Cold Shower Bath** is an effective tonic, being useful in mania, hysteria, sunstroke, etc. **Needle Bath** is a shower bath thrown in a fine spray.

4. **Cold Sitz-Bath or Cold Hip-Bath.**—In this the person sits in a tub with the water up to his hips. The vessels of the cooled surface and intestines first contract and then dilate, especially when friction is applied.

5. **Cold Foot-Bath** tones the system and strengthens the feet, but is to be avoided during the menstrual period.

6. **Cold Wet-Sheet Pack** is done thus:—Spread two blankets over the bed taking care to cover the pillow. Thoroughly wet a bed-sheet and spread it over them. Strip the patient naked and make him lie flat on the sheet. Wrap him up tightly in the sheet and blankets, the ends of the sheet being carefully tucked in on each side and the feet covered. Cover him with two or more blankets, the face being left open. After a short feeling of chilliness the patient experiences a delightful glow followed by copious perspiration, thereby reducing the temperature, delirium, and irritability. After $\frac{1}{2}$ to 1 hour the packing is removed and the body well rubbed with dry towels.

Instead of cold, tepid or warm water may be substituted. The above description applies to **general packing**, which is usefully employed in specific fevers, such as measles, scarlatina, small-pox, etc., to help the development of the rash, or to bring it out if it has receded. To reduce delirium, excitement, and hyperpyrexia, and in mania and insomnia, it is always useful. A local wet pack can be used in pneumonia, chronic diarrhoea, etc. A cold compress round the throat checks the inflammation of acute tonsillitis, whilst a similar compress on the stomach will often check obstinate vomiting.

7. **Cold Douche.**—In this a single stream of water is forcibly directed against a part of the body. Its effects depend mainly upon the size, height, and temperature of the stream, as well as the extent of the surface affected. The douche can be usefully directed against (a) *head*, in alcoholic coma and narcotic poisoning; (b) the *spine*, in spermatorrhoea, melancholia, and general debility; (c) *liver* and *spleen*, for chronic congestion and enlargement; (d) the *joints*, for chronic inflammation and stiffness; (e) the *perineum*, in which case an ascending douche with a rose is used in pruritus ani, hæmorrhoids and spermatorrhoea; (f) the *vagina* in leucorrhoea; (g) *rectum*, in constipation and hæmorrhage.

8. **Cold Sponging.**—In this the surface of the body is freely sponged over while the patient is sitting or standing on a shallow tub. It has a tonic and bracing effect.

9. **Ice Bag and Leiter's Coil.**—For local application of cold to the head, chest, or abdomen, an india-rubber bag filled with ice or a closely wound coil of metal tubing through which a continuous stream of water is allowed to flow may be applied.

10. A **Freezing Mixture** consisting of powdered ice 2 parts, common salt 1 part, is very useful in minor operations and in chronic rheumatism. It causes anæsthesia and may vesicate if left too long in contact with the skin.

B. Warm or Hot Bath.—It may be either *medicated* or *non-medicated*, general or local. It (a) softens the dermis and liquefies the fatty secretions and hence acts as a good detergent in many scaly and scabby skin diseases; (b) stimulates local circulation and lessens

that of the internal organs, whereby relieves pain of intestinal, biliary, and renal colics; (*c*) relaxes tissues and relieves muscular spasms in urethral stricture, colic, laryngeal spasm, hernia, infantile convulsions, etc.; and (*d*) stimulates the secretion of sudoriferous glands, by which many kidney diseases are benefited and uræmia may be averted.

Great care should be taken during and after a hot bath. The patient must be quickly dried, covered, and put in a warm bed. A cup of hot tea, hot milk, or hot water greatly helps diaphoresis.

1. **Tepid Bath.**—Temp 85° to 95° F. it has a detergent, sedative and antipyretic effect. Useful in pyrexia and restlessness

2. **Warm Bath.**—Temp. 95° to 100° F. Used in fevers, threatening inflammatory affections, etc., as bronchitis, pneumonia

3. **Hot Bath**—Temp. 100° to 106° F. Action is the same as above, but more powerful.

4. **Hot Foot-Bath.**—To arrest threatened catarrh, cold in the head, epistaxis, infantile convulsion and to restore menstrual flow stopped by cold.

5. **Hot Sitz-bath**—Useful in amenorrhœa, dysmenorrhœa, sudden cessation of menstruation from cold, dysuria, cystitis, etc. The addition of a little mustard helps to re-establish the menstrual flow more quickly.

6. **Hot-water Sponging.**—Sponging the head, temples, and neck with hot water relieves the headache in influenza, catarrh, and other diseases.

7. **Hot Douche**—A very hot uterine douche, temperature between 110° and 115° F. is a good method for checking post-partum hæmorrhage.

C. **Medicated Baths.**—In these, medicinal agents are dissolved in cold or warm water. They may be divided into the following:—

1. **Sea Bath.**—On account of the various saline ingredients held in solution, sea-bathing is especially invigorating and stimulating to the skin. Moreover, the temperature being more or less uniform, sea-bathing is more easily borne by the weak than river-bathing.

2. **Carbonic Acid Bath.**—This is a stimulating saline bath containing sodium chloride 3 p.c., calcium chloride 1 p.c., carbonic acid gas (free) up to 3 grammes to 1 litre. Recommended in heart disease either functional or organic. The effect of the *Nauheim Bath* is due to its saline and gaseous constituents.

3. **Acid Bath**—In this a flannel roller 1 foot broad is soaked in a bath containing diluted nitro-hydrochloric acid 8 ozs in 1 gallon of water at 98° F, and wrapped twice round the hepatic region, after wringing out the superfluous lotion. It is then completely covered by a piece of oiled silk leaving a little margin. The bath should be renewed morning and evening and worn for days. Useful in hepatic disorders.

4. **Alkaline Bath** is made by dissolving crystallised sodium carbonate (60 grs. to 1 gal) in water, and is useful in removing scabs and scaly incrustations.

5. **Mustard Bath** (30 to 60 grs. to 1 gallon).—A powerful stimulant to the skin, used to quicken the appearance of exanthematous eruptions. The patient should remain in the bath from 5 to 10 minutes.

6. **Bran Bath.**—Bran 4 lbs. are boiled in water 1 gallon, and strained. This liquor is added to water sufficient for a bath. It removes irritation of the skin

7. **Neem Bath**—It is prepared by adding the decoction of leaves of *Melha azadirachta* to the ordinary bath. It may be general or local, and is largely employed in India in various skin diseases.

8. **Mineral Water Bath.**—A course of baths in any of the spas has special advantages. The effects of a bath in simple thermal water are similar to those derived from an ordinary warm bath; but they differ according to the composition of the mineral waters. Thus

bathing in and drinking sulphur water are very efficacious in chronic rheumatism, gout, hepatic congestion, etc.

D. Vapour Bath.—This may be aqueous or medicated. A **Steam Bath** may be made by boiling water over a spirit-lamp under a cane-bottomed chair, on which the patient sits, enveloped completely, except the head, by one or two blankets. Action and uses are the same as those of hot water bath. The **Russian Bath** consists in exposure of the body to moist vapour at different temperatures. It is said to be risky to persons with weak hearts, and there is certainly more danger of heat stroke than in the **Turkish Bath**, in which only dry air is used. Either of these baths is useful in rheumatism, gout, malaria, renal and skin diseases.

E. Air Bath—Hot-air bath may be employed like a steam bath, by simply arranging a few electric bulbs connected by wires inside the frame-work which supports the bed clothes, or by passing hot air.

SCALE OF TEMPERATURE OF BATHS (Startin)

Bath	Water	Vapour	Hot Air
Cold	33° to 65° F.		
Cool	65° to 75° F.		
Temperate	75° to 85° F.		
Tepid	85° to 92° F.	90° to 100° F.	96° to 106° F.
Warm	92° to 98° F.	100° to 115° F.	106° to 120° F.
Hot	98° to 112° F.	115° to 140° F.	120° to 170° F.

Bolus.—A bolus is a large pill containing over 10 grains of powdered ingredients. The most convenient plan when a large dose of a nauseous powder is to be administered, is to give it in a cachet, or wafer paper.

Buginaria.—Bougies are elongated cylindrical preparations containing active drugs mixed with the suppository basis for introduction into the urethral and the nasal cavities. Bougies are made like suppositories but differ from them in shape.

Antrophores are medicated bougies containing a spiral spring wound with fine wire, and coated first with an insoluble layer of white gelatin and then with a diluted mucilage. They may be medicated with cocaine, iodoform, protargol, etc.

Cachets are wafer paper capsules. They consist of two concave or watch-glass shaped halves or discs of wafer paper stuck together at the rims by moisture. Any nauseous or bitter drug can be thus enclosed between the two halves and swallowed without being tasted. Cachets should be dipped in water immediately before swallowing.

Capsules.—A capsule is a gelatin sac enveloping a dose of some nauseous or disagreeable drug.

Carbasa Antiseptica.—Antiseptic Gauzes are mulmuls steeped in some antiseptic solution and dried afterwards. The following is the process for an extemporaneous preparation. Take 2 yards of gauze having 30 threads to the linear inch, hang it over a string, and spray over it uniformly the required volume of antiseptic solution on each side, turning once or twice until the whole of it is used. Or the folded gauze may be dipped into the solution in a deep dish, and turned over and over until the whole of it is equally absorbed and then taken out, unfolded, dried and sterilised.

Collunaria are lotions used as nasal douches.

Collutories are throat or mouth paints; as *Glycerinum Acidi Borici*. *Collutoire* is a French term

Collyria are eye-lotions or eye-washes. Sometimes they are called eye-drops.

Cremora.—Creams are soft or semi-liquid preparations for external

application, having glycerin, soft paraffin or some similar substances as a basis, *e.g.* Cold Cream.

Elæosacchara. Aromatic Sugar or Oil Sugars.—These are more common on the Continent than in England, and are made by triturating 9 minims of volatile oils to 1 oz. of sugar. They are used as flavouring agents.

Enemata. Enemas. Clysters. Lavements. Rectal Injections.—A liquid preparation introduced into or through the rectum by means of a suitable instrument is called an enema.

If the injection is meant to evacuate the bowels, 1 to 2 pints of liquid are injected, the patient lying on his left side; but when it is intended that it should be retained, a small quantity (2 to 4 ozs.) should be used. If it is considered desirable to introduce 3 to 6 pints, the liquid must be slowly thrown up the bowel while the patient is lying first on his left, then on his right side with his pelvis raised, or, if necessary on his knees and elbows, pressing the anus with a towel whenever there are expulsive cramps. This is best done by slowly pouring the fluid into a funnel to which a long gum-elastic tube is attached. It then flows steadily as the result of hydrostatic pressure and is less likely to be ejected. This process is called **Enteroclysis**. It must be borne in mind that the process of injection should be carried on slowly and with occasional pauses, otherwise the enema will be expelled by premature contraction of the intestine. The temperature of the liquid should be 98° F. Cold water is soon rejected.

The following are the chief varieties of enemas with their uses:—

1. **Anthelmintic Enemata** are chiefly used to expel thread-worms, *e.g.* infusion of quassia or hypertonic saline.

2. **Antispasmodic Enemata**—For this purpose an injection of Oil of Turpentine, Asafetida (Tr. asafœtida 6 to 12 p.c. in mucilage of starch), Bromides (pot. bromide 1 p.c. with acetyl salicylic acid 0·5 p.c., and mucilage tragacanth, in normal saline), etc., is given when the intestine is distended with flatus, or getting cramped.

3. **Astringent Enemata.**—These are used for checking diarrhœa, rectal hæmorrhage, and mucus discharge from the rectum and lower bowels.

4. **Emollient Enemata.**—A decoction of starch, linseed, or barley soothes the irritable mucous membrane of the rectum and colon.

5. **Sedative Enemata.**—These are used in painful affections of the rectum, *e.g.* Tr. opii 0·5 to 6 p.c. in mucilage of starch.

6. **Purgative Enemata**—These are often resorted to when the lower bowels are to be evacuated. Ordinarily, for an adult 1 pint, for a child of four years of age 4 to 6 ozs., and for an infant 1 oz., are enough. Soap and warm water, thin gruel, and castor oil or olive oil, etc., are often used for this purpose. Glycerin 2 to 4 drs with an equal amount of warm water injected by means of a suitable syringe, or a glycerin suppository introduced into the rectum, evacuate the bowels speedily.

7. **Nutrient Enemata**—In case where food cannot be swallowed by the mouth, or retained by the stomach, liquid glucose or dextrose 10 p.c. with normal saline may be given per rectum, not more than 4 oz. at a time. Before the nutrient enema is given the bowel should be washed out each *morning with tepid water*.

Fomenta.—Fomentations consist of flannels, cloths, or sponges wrung out of hot water to which a drug may or may not have been added, for application to the surface of the body.

The proper way to apply fomentations is to take a twofold piece of flannel large enough to cover the affected part. Immerse this folded flannel in a kettle of boiling water or pour boiling water over it in a basin, and lift it by a pair of tongs or a stick, and put it on a wringer—a stout towel or duster with sticks attached to both ends. The water is then squeezed out as much as possible and the flannel

applied to the affected part and covered with a large piece of india-rubber sheeting or oiled silk, extending about an inch beyond the flannel. Place over this a thick layer of cotton-wool and bandage. If the full effect of fomentation is desired the flannel should be changed every 20 or 30 minutes. In the case of the feet, hands or forearms, dipping them in hot water may do, but its temperature should be maintained by frequent small additions of boiling water.

If it is desired to produce a counter-irritation, oil of turpentine may be sprinkled over the flannel before application. This forms the turpentine-stupe. For an anodyne or sedative action, laudanum may be sprinkled in the same way, or a few poppy-heads or a little opium may be put into the water before boiling.

Dry fomentation is made by filling bags with hot bran, salt, sand, or chamomile flowers. Bottles filled with hot water and covered with flannel bags or old stockings may be used for dry fomentation. A piece of flannel roasted over fire and applied also serves the purpose.

Hot Antiseptic Compresses.—These consist of folds of lint or cloth soaked in hot antiseptic lotions and covered with a piece of waterproof, oiled silk, or guttapercha tissue; as Boric Acid Compress.

Fumigation is a local or general bath of volatilised drugs. Sulphur and mercury are chiefly used for this purpose. Mercurial fumigation, either *general* or *local*, has long been used in the treatment of secondary syphilis.

Gargarismata. Gargles.—A gargle is a liquid preparation used for topical action on the mouth, throat, and pharynx. A gargle may be any of the following kinds:—

1. Stimulant Gargle, that stimulates the mucous membrane and glands; as Capsicum (Tr. Capsicum 2 drs. to Water 8 ozs.), Myrrh, Eucalyptus Gum (120 grs. to 8 ozs.), etc. These gargles often relieve deafness due to obstruction of the eustachian tube by increased pharyngeal secretion.

2. Astringent Gargle, that checks excessive secretion; as iron salts, zinc salts, alum (12·5 p.c.), tannic acid (30 grs. to 8 ozs.), astringent infusions, etc.

3. Antiseptic Gargle, that removes foul secretions and odours; as carbolic acid (5 p.c.), boric acid, potassium permanganate (0·025 p.c.), etc.

4. Demulcent Gargle, that removes burning and irritation; as barley water, linseed tea, ispaghul seed tea, milk, etc.

Gossypia Antiseptica.—Antiseptic Cottons are made by charging absorbent cotton-wool with various antiseptic drugs. This is done by soaking cotton in some saturated antiseptic fluid and afterwards drying it; as Gossip. Acid, Borici, Gossip. Acid, Salicylici, etc.

Guttæ.—Drops are liquid preparations used as drops; as eye-drops, drops for the ear, etc.

Haustus. Draught.—A liquid preparation or mixture when taken in a single dose is called a draught; as castor oil draught; hydrate of chloral draught, etc.

Insufflations are powders blown into the throat, nostrils, or larynx. Laryngeal insufflation can be managed thus:—Vulcanite tube curved at a suitable angle, having an aperture covered by a slide, through which the medicinal powder is introduced, is carried over the tongue to the laryngeal orifice, and the powder is either blown in by the mouth or by an elastic bulb attached to the end of the tube. This instrument is called “Pulveriflator.” A quill or a tube half filled with powder and blown by the mouth may do for nostrils and throat.

Jujubes are lozenges made of gum acacia and sugar. They are prepared by boiling to a suitable consistence, gum acacia 16 lbs., sugar 7 lbs. and water $\frac{1}{2}$ gal. They are sometimes covered with a coating of crystallised sugar.

Linctus.—Lincture or Loch is a thin confection to be slowly swallowed in small doses, so as to act on the throat. The basis of

linctus is either treacle, syrup, honey, or any other sweet viscid substance. When powders are the active ingredients they should be made very fine, before admixture with the basis.

Massæ.—Masses consist of ingredients mixed together to the consistence of a pill. They are official in the U.S.P.

Mollinum is an ointment prepared with mollin or superfatted soap. It is easily washed off with water forming a lather and leaves the skin fresh and supple. As *mollinum Hydrargyri*. Mollin contains 17 p.c. of uncombined fat and 30 p.c. of glycerin.

Nebulæ are solutions of drugs in aqueous, oily, alcoholic, or glycerinated media to be sprayed into the throat by the help of a spray-producer; as *Nebula Adrenalinæ et Cocainæ*.

Opodeldocs or **Saponimenta** are preparations having as their basis soap liniment. Medicated opodeldocs are official in Continental Pharmacopœias.

Pastillus or **Pastil** is a soft jujube variously medicated, having glyco-gelatin as its basis instead of gum acacia and sugar. These are used like lozenges. As *Pastilli Mentholis*.

Perles are minute pills.

Pessi.—**Pessaries** resemble suppositories, but are intended for introduction into the vagina.

Pigmenta.—**Paints** are liquid preparations used for application to the throat, skin or other parts. A pigment differs from a collutoire in that the former is used as a paint for any part of the body, whereas the latter is for brushing the throat or mouth only. As, *Pigmentum Chrysarobini*, *Pigmentum Iodi* Co.

Sprays are liquid preparations intended for application to the upper air passages through an atomizer.

Steatina.—**Steatins**, **Ung Extensa** or **Salve Mulls** are ointments of a hard consistence spread on muslin, and capable of being folded and cut at pleasure. Mutton or beef suet form their principal basis.

Sticks or **Pencils** are solid cylindrical rods prepared by fusing drugs and pouring the melted mass into suitable moulds; as toughened and mitigated caustics. When the melted mass is poured into a conical mould it is called a cone; as a *Menthol Cone*.

Styles are thin bougies about 2 inches long for introduction into the lachrymal sac and nasal duct.

Triturationes.—**Triturations** are solid dilutions. These are intimate mixtures of substances with lactose.

Varnishes are preparations which, when applied to the skin, evaporate and leave a coating. Varnishes are often medicated.

Vina or **wines** are weak tinctures prepared with sherry. They were official in B.P. 1914.

Wafer papers are used to wrap round nauseous or bitter powders to disguise their taste. They are made of flour and water, and become limp when moist. **Cachets** consist of the same material.

PART II

ADMINISTRATION OF DRUGS

CHANNELS FOR ADMINISTRATION OF DRUGS

THE following are the various channels through which drugs can be introduced into the system either for their local action or for systemic effects after absorption :—

1. **The Digestive tract** is the most important and the ordinarily selected route.

(a) *The Mouth*.—We administer drugs by this route either for their absorption by the alimentary tract, or for their local action. Sometimes drugs produce systemic effect through absorption by the mucous membrane of the mouth. Nitroglycerin is often used by this route, and is more effective than when swallowed, because it avoids the portal circulation. *Sublingual* administration of adrenaline is adopted to avoid decomposition of the drug in the stomach. For local action we use gargles, paints, pastilles, lozenges, etc.

(b) *The pharynx* is reached by pigments, pastilles, collutories, sprays, insufflations, lozenges, jujubes.

(c) *The Stomach and Intestine*.—Drugs are administered by this route either for their local action on the stomach and intestine, or for their systemic effect after absorption. Absorption of drugs from the stomach is relatively small and it does not really occur till the drug has reached the small intestine. For local effect on the stomach, digestive ferments, direct emetics, or gastric sedatives are generally used. Purgatives are used for their effect on the intestine and these unfold their action on reaching this part of the gut. Sometimes drugs are administered for action on the intestine and not intended to be dissolved or decomposed in the stomach. Such drugs are administered in keratin coated or salol varnished pills.

Some drugs are so altered or decomposed during their sojourn in the stomach and intestine that oral administration of such drugs is not followed by any pharmacological effect, while others are too irritant to be used by this route. These are adrenaline, antitoxins, arsphenamine, emetine, etc

But the greatest use of drugs by this route is for their systemic effect after absorption. The absorption of a drug is influenced by (i) its *solubility*, and (ii) the *conditions under which it is administered*. Thus, a pill takes a longer time to be absorbed than a mixture. Again, salines are more rapidly absorbed than metallic salts or alkaloids. A drug acts more rapidly on an empty stomach than on a full one. On an

empty stomach with a healthy mucous membrane crystalloids in solution pass readily through the vessel walls. Colloids on the other hand require to be digested and emulsified before they can be taken up by the blood-vessels and the lacteals. Mixtures, draughts, pills, powders, boluses, emulsions and confections are administered by this route.

(d) *The Rectum*.—Drugs are sometimes administered by this channel either for action after absorption, or for their local action on the bowel, *e.g.* suppositories, enemas, etc. This route is used to avoid the action of a drug on the stomach and intestine, and since it has a good absorbing surface with its vascularity and venous plexuses, many soluble substances produce their effect more quickly and without passing through the liver where they are likely to be destroyed. Certain anæsthetics and hypnotics are also introduced by this route, *e.g.* ether, paraldehyde, etc.; nutrients (*e.g.* glucose) and saline solution are administered per rectum to maintain the strength of the patient, to counteract toxæmia, or to keep up the action of the kidneys.

2 The Respiratory tract is the next most important route.

(a) *The Nose*.—Drugs are administered by this route either for their local action in the nose or the lungs; or for reflexly stimulating the heart and respiration, or for systemic effect after absorption. Inhalation is carried on by the nose and the mouth. For local action we use collunaria, snuffs, bougies, paints, insufflations or sprays and nasal lavage. Sometimes drugs are sprayed into the nose for action after absorption, *e.g.* the use of pituitary extract in the treatment of diabetes insipidus.

(b) *The Larynx* is reached by inhalations, insufflations, sprays and pigments.

(c) *The Lungs*.—Through this channel vapours or atomised drugs rapidly enter the system. Ether, chloroform, and other gaseous anæsthetics are used to produce general anæsthesia after absorption from the lung surface; CO₂ is used to stimulate the respiratory centre; and various antiseptics are used in septic conditions of the lungs for their local effects. Iodised oil is introduced to visualise the condition of the lungs and the bronchioles under X-rays.

3. The Skin —By the following methods, we can introduce medicaments into the body through the cutaneous surface:—

(a) *Enepidermic*.—In this method, drugs are simply kept in contact with the unbroken skin without friction or rubbing. Pastes, plasters, poultices, fomentations, pigments, creams, ointments, etc., are thus applied.

(b) *Epidermic, Iatroleptic or Inunction*.—In this method drugs are rubbed into the unbroken skin to promote their

passage between the cells of the epidermis. For this purpose the drugs are either dissolved or mixed with oils or fatty substances. Familiar examples are the cod-liver oil inunction in the treatment of rickets, and the use of blue ointment in the treatment of syphilis. The method is best suited for children, or for persons who cannot take oils by the mouth.

(c) *Cataphoresis* or *Ionic Medication*.—Some salts when in solution split up into their component molecules or ions. When a constant electric current is passed through them, the metallic ions and basic radicles are driven away from the positive pole, the acid radicles are driven away from the negative pole. This is utilised in medicine by soaking a thick pad in the solution of the drug to be used, attaching the negative pole of the pad when one desires to drive acid radicles to the tissues, the positive pole being on a neutral part. The exact opposite holds good when basic radicles have to be driven into tissues.

(d) *Intradermal* or *intracutaneous* injection is the introduction of substances between the layers of the skin. This is done in certain skin tests, as the Schick test for diphtheria, or for the production of infiltration anaesthesia.

(e) *Inoculation*.—In this the epidermis is punctured or scarified for introduction of medicaments; as vaccination.

4 **The Subcutaneous Tissues.**—These are reached by hypodermic or subcutaneous injections, which is effected by a small syringe to which is attached a fine hollow needle. This is generally done on the forearm, arm, thigh, etc., but when a large quantity is used, *e.g.* saline or antitoxins, the loose areolar tissue of the subscapular region or the mammary region is selected. By this method the drug is quickly absorbed by the lymphatics and the blood-vessels, and any possible reaction in the stomach which may destroy its effect is avoided. Moreover one knows exactly the quantity of drug introduced into the system. It has however the disadvantage of forming abscess, which may be sterile from irritant drugs, or septic due to infection from faulty technique.

Hypodermoclysis is the introduction of large quantities of fluids into the subcutaneous tissue, as injection of saline or glucose solutions.

5. **The Deep Tissues.**—By the same instrument drugs can be introduced into the deeper structures, *e.g.* the muscles and nerves. When the injection is given into the muscles it is called *intramuscular injection*, and is generally given into the gluteal muscle. Intramuscular injections are given when the quantity to be injected is large, or when suspensions of insoluble drugs are used. The object is to form depots for gradual absorption and continued action of a drug. Apart from the precautions necessary for all injections, the possibility of injecting the drug into a vein,

or puncturing a nerve, should be kept in mind. Cases are on record where much harm has been done by injecting an irritant drug into a nerve. Familiar examples of intramuscular injections are those of calomel or bismuth in the treatment of syphilis.

6. **The Blood-vessels.**—Through these channels, blood and saline fluid are *transfused*, and drugs are administered *intravenously*. It is the most rapid and certain way of bringing drugs into the circulation and tissues, and is generally used when a definite concentration of the drug is required very rapidly. Thus, during an emergency, when immediate action is necessary it is largely used, *e.g.* intravenous injection of saline solution in the treatment of collapse of cholera; of strophanthin in cardiac failure; of glucose and insulin in diabetic coma. It is also used for certain drugs which are either decomposed in the digestive tract, or are too irritant to the stomach and subcutaneous tissues. Well-known examples are the uses of antimony preparations in the treatment of kala-azar; neoarsphenamine in the treatment of syphilis; and tryparsamide in the treatment of trypanosomiasis. This route is also selected to secure direct action on the infecting organism in the blood stream, *e.g.* the use of quinine in malignant malaria. The drugs used by this route must be in complete solution and must not react with the proteins of the blood. Unless there be definite indications, this route should be avoided. Injection of foreign substances directly into the blood alters the equilibrium of the colloids which in itself may cause alarming symptoms by producing fall of blood pressure or even fatal reaction.

Acids and metallic salts being incompatible with blood should not be used by this route. Moreover irritant substances may produce thrombosis, inflammation or fibrosis of the veins. It should be avoided in greatly debilitated persons, the old, those suffering from high blood pressure, and who are subject to anaphylactic shock.

Intravenous administration is commonly used for the following purposes:—

(a) *To bring about certain changes in the blood*; either in volume, in reaction or coagulability. Drugs commonly used are, saline solution, glucose, sodium bicarbonate, calcium salts, etc.

(b) *In the treatment of bacterial invasion*; *e.g.* iodine, hexamine, mercurochrome and sulphonamides.

(c) *As specifics in certain protozoal infection*; organic arsenic compounds, antimony compounds, quinine, etc.

(d) *In cardiac and circulatory failure*; Strophanthin, adrenaline, etc.

(e) *To produce general anaesthesia*; evipan sodium, magnesium sulphate, etc.

(f) *As diagnostic agents*; uroselectan B, indigocarmine, tetraiodophenolphthalein.

(g) *As sclerosing agents in varicose veins*; sodium morrhuate, quinine urea, etc.

7. **The Serous Cavities.**—These are only useful when the local action of the drug is required.

FACTORS MODIFYING THE ACTION OF DRUGS 47

(a) *The Pleura*.—In empyema, we can wash out the pleural cavity with antiseptic lotions.

(b) *The Peritoneum*.—An injection of saline solution has been advocated in conditions of collapse. The peritoneum may be washed out with antiseptic fluids in some varieties of peritonitis.

(c) *The Tunica Vaginalis*—Solution of iodine, liquefied phenol or sodium morrhuate are sometimes injected to produce an adhesive inflammation in hydrocele.

8. *The Conjunctivæ and Lachrymal Ducts*.—Mydriatics, myotics, and drugs for local action on the conjunctivæ and lachrymal ducts are applied either as collyria, ointments or powders.

9. *The Ear* is reached by injections, drops, insufflations, etc.

10. *The Bladder and Urethra* by injections and bougies.

11. *The Vagina and Uterus* by douches, injections, pigments, pessaries, medicated cottons, etc.

12. *Superior longitudinal sinus* is often punctured to introduce drugs in cases of infants when other veins are not accessible. This corresponds to intravenous injection.

13. *Intraspinal injection* through lumbar puncture is done for the treatment of cerebrospinal meningitis with antimeningococcal serum, for the production of spinal anæsthesia, or for the introduction of magnesium sulphate or antitetanic serum in the treatment of tetanus. Diffusible substances are readily absorbed from the subarachnoid space.

14. *Intraventricular injection* is done after trephining the skull in cases where the ventricles are to be reached. In infants under 18 months this can be reached through the anterior fontanelle.

15. *Intracardiac injection* is resorted to in case of sudden stoppage of an otherwise healthy heart. The best example is the intracardiac injection of adrenaline in collapse under anæsthesia, carbon monoxide poisoning, etc.

FACTORS MODIFYING THE ACTION OF DRUGS

Many factors modify the action of a drug. Therefore having selected a drug and the route through which it is intended to be administered, it is necessary that the student should recognise the different factors, as the dose has to be modified or regulated under these circumstances.

The word "dose" as ordinarily understood, means the quantity of a drug which is necessary to produce a certain pharmacological action either at once or after repetition. By a *maximum dose*, is understood the largest quantity which may be given to an adult without producing evil effects; and by a *minimum dose*, the lowest quantity which is necessary to obtain a physiological action. The B.P. doses represent only average ordinary doses for an adult.

The student should bear in mind that the action of a drug varies with different doses. Thus, tartarated antimony is a diaphoretic in $\frac{1}{32}$ to $\frac{1}{8}$ gr., and an emetic in $\frac{1}{2}$ to 1 gr. doses; ipecacuanha powder is an expectorant in $\frac{1}{2}$ to 2 grs., and emetic in 15 to 30 grs. Though the B.P. posology is meant as a general guide, yet the practitioner can reduce the minimum and exceed the maximum limits of the pharmacopœial doses.

The other factors which require consideration in regulating the dose are:—

1. **Age.**—The dosage varies considerably with the age. By *Adult dose* is meant the dose for a person between 20 and 60 years of age. Children should get a fractional part of the adult dose. A practical method of calculating the children's doses under 12 years is given by Young. *The rule is to divide the age in years by the age in years plus 12; the resulting quotient is the proper fraction of an adult dose.* Thus the dose

for a child of 1 year, will be $\frac{1}{1+12} = \frac{1}{13}$ of an adult dose

„ 4 years „ $\frac{4}{4+12} = \frac{1}{4}$ „

Conling's Rule.—Adult dose $\times \frac{\text{age next birth day}}{24}$

The dose for a child of three years old will be $\frac{4}{24}$ or $\frac{1}{6}$ of adult dose.

Dilling's formula is $\frac{\text{age}}{20}$ when calculating with metric weights.

From 12 to 16 years, $\frac{1}{2}$ to $\frac{3}{4}$, and from 17 to 20, $\frac{3}{4}$ to $\frac{4}{5}$, are the proportions. Over 60 years, the dosage should again be diminished slightly. For hypodermic medication, the dose is one-half of what is given by the mouth, and for rectal medication, it is the normal dose plus one-fourth, except in the case of strychnine, which should be exhibited in smaller quantities than when given by the mouth.

2. **Sex.**—Women, as a rule being more delicate than men, cannot bear full adult doses. The menstrual period should also be taken into consideration. For instance quinine, if given during the period, may cause alarming hæmorrhage. Similarly strong purgatives should be avoided during pregnancy or used with care and judgement because of their tendency to cause pelvic congestion which may lead to miscarriage. For the same reason drugs acting on the uterus should also be used with caution. Many drugs are excreted with milk and this should be remembered when treating nursing mothers. Moreover many drugs pass from

the mother to the foetus, and drugs which may not have any effect on the mother may produce a more serious effect on the child.

3. **Size and Body Weight.**—The quantity which is required to produce a certain physiological effect in a strong, healthy and stout person of more than average size and weight, is not necessary to produce the same action on a thin and weak individual.

4. **Idiosyncrasy.**—Individual susceptibility to the action of a particular drug or drugs has long been recognised; and the unusual or peculiar reaction to a drug is known as *idiosyncrasy*. This may be either too much action, too little action, or an abnormal action not ordinarily observed. Thus we often come across patients who cannot take a small dose of potassium iodide without coryza, though ordinarily many can take it in large doses without inconvenience. Others again are salivated by quite small doses of mercury.

Although one form of idiosyncrasy is shown by increased action of a drug, instances are also common when a drug fails to produce any effect even in comparatively large doses. This form of idiosyncrasy is known as **tolerance**, and when this tolerance exists from birth it is called **congenital or natural tolerance**.

Again certain drugs fail to produce the same effects with the same dose when continued for a lengthened period. This is often found with opium. The dose requires to be increased after some time to get the full or the original effects of the drug. This gradual loss of activity is due to **acquired tolerance**. Sometimes the person taking it becomes so addicted to its use that he actually craves for or indulges in it, to the detriment of his health. This craving for the particular drug is called a **habit**; and the drug is known as **habit forming drug**. Persons may contract alcohol habit, heroin habit, cocaine habit, etc.

The toleration is possibly due to (a) rapid elimination (atropine in cats); (b) diminished absorption (arsenic); (c) destruction of the poison (morphine); (d) the formation of some antitoxin; or (e) the capacity of the body to fix the poison in some non-toxic form.

Although the term tolerance is used with regard to certain drugs, it is also used nowadays to denote the peculiar form of partial immunity that is developed in certain protozoal diseases like malaria. As a result of repeated infection and reinfection a condition is established in which the host is able to live a more or less healthy life and to offer some resistance to reinfection while still harbouring the parasites in small number. This type of infection immunity is also known as *premunition*.

Racial idiosyncrasy is often noticed and different species of animals vary in their action to different drugs. Thus

rodents are immune to the action of emetics; atropine does not quicken the heart in rabbits, etc. It is possible that the failure to react to atropine is due to its destruction in the blood or to the fact that the vagus is not active in rabbits.

Allergy or hypersensibility is also a type of idiosyncrasy and applies both to drugs and food. Although allied to anaphylaxis the reaction does not usually desensitise. It often runs in families and is manifested by the appearance of urticarial rash, œdema, spasm of smooth muscles, etc. The cause of allergic reaction is not clearly understood, although deficiency of calcium in the tissues renders the whole autonomic nervous system susceptible to the action of certain drugs.

5. Rate of Absorption and Excretion.—The action of a drug depends upon the concentration in the tissue fluids around the organ on which it produces its effects. It follows therefore that when a drug is administered its effects will depend upon the rapidity of absorption and excretion. Administered intravenously a drug acts most quickly than when given by other routes. In most cases however the intramuscular or subcutaneous injections produce quicker effect than when given by the oral route where the action depends upon the rate of absorption and this is influenced by many factors. The action of a drug and the duration of its effect therefore depend upon many factors, viz. rate of excretion, fixation by the tissues, detoxication by oxidation or reduction, or formation of some inert body.

The chief channel of excretion is the kidney, but the rate of excretion of different drugs by this channel is variable, and drugs which are excreted slowly tend to accumulate in the system and produce toxic symptoms. Although the kidney forms the chief channel of excretion, many drugs, notably the metals, morphine, etc., are eliminated by the fæces.

6. Mental Condition.—A morbid inclination of the mind towards the action of a particular drug increases the action of the same. Thus, if a patient can be convinced that he will sleep by a certain draught, small doses of a hypnotic may induce sleep.

Temperament has some influence on doses. A person with a sanguine or nervous temperament requires smaller doses than one with a lymphatic one.

7. Fasting.—A drug acts more powerfully on an empty stomach than on a full one. Thus the same quantity of alcohol, which would intoxicate a person if taken on an empty stomach, can be ingested with impunity if taken during or after meals.

8. Disease.—Many diseases considerably modify the dosage of medicines. Thus, opium is borne in surprisingly large doses in biliary and renal colics. Large doses of mercury are tolerated in syphilis.

9. **Climate.**—It is a well-known fact that alcohol can be consumed in larger quantities in cold countries than in hot climates.

10. **Time of Administration.**—Vital force is lowest at the early hours of the morning. Consequently, in debilitating diseases, simulants are more necessary at this time than later on in the day. It is useless to administer even a very large dose of chloral hydrate when the person is up and about; it should be given at bedtime. Cod-liver oil should always be given after food; given at any other time it may derange digestion. To avoid irritation of the stomach, iron and arsenic should always be given on a full stomach. Saline purgatives which act quickly when given on empty stomach are best administered early in the morning. The more slowly acting purgatives like aloes, etc., are given at bedtime.

11. **Accumulation.**—Ordinarily a drug after introduction into the body is either slowly or rapidly excreted. But if we continue to administer it very frequently for a sufficient length of time, *i.e.* so quickly that it cannot be fully eliminated, or the tissues fail to detoxicate it, a time may come when it will accumulate to such an extent as to produce suddenly toxic symptoms. Drugs which produce symptoms of chronic poisoning are also cumulative and the symptoms are the result of cumulative action. It may be caused by the following circumstances:—

(a) *Rapid absorption and slow elimination of a drug.*—This is generally observed with most metals which are not only excreted slowly but the tissues cannot destroy or detoxicate them. Well-known examples are mercury and lead.

(b) *Slow excretion due to fixation of the drug in the tissues.*—Digitalis is cited as an example of this class. During a course of digitalis treatment, if no precaution is taken, symptoms of poisoning may suddenly develop without any increase of the dose. This is due to the fact that the body destroys or eliminates an equivalent of 1 to 2 c.c. of the tincture daily. If therefore a patient is treated with 2 to 3 c.c. of digitalis tincture daily, sufficient amount may accumulate in the body after some time to produce toxic effects. It is therefore necessary that after full digitalisation the *maintenance dose* should not exceed 1 c.c. daily.

(c) *Sudden solution and absorption of a sparingly soluble drug owing to some changes in the contents of the intestine.*

ANTAGONISM AND SYNERGISM

By antagonism is meant the weakening or prevention of the action of a drug by that of another. An antagonist may be a drug, or a substance formed in the body. They may act by (1) *Detoxication*, *i.e.* by chemical combination with

one another, *e.g.* free acids and alkaline carbonates, oxalates and lime salts. (2) *True antagonism*. Here the drugs have no chemical affinities for, nor do they react with, each other, but produce opposite effects by acting either on (a) *the same structures*, as pilocarpine and atropine, the former stimulates the parasympathetic endings while atropine depresses them; or (b) *different structures*, *e.g.* adrenaline and amyl nitrite; the former constricts the vessels by stimulating the nerve-endings, while the latter dilates the vessels by direct action on the muscles.

Just as the weakening or prevention of the action of one drug by that of another is known as antagonism, the one-sided or reciprocal augmentation of such action is known as *synergism* or *potentiation*. For example magnesium sulphate and sulphuric acid make a stronger purgative than magnesium sulphate alone. It has been found that doses of cocaine which by themselves produce no appreciable effects, very markedly increase the effects of adrenaline on the vessels, the dilator of the iris, etc. Bromide and chloral hydrate make a better hypnotic than either used alone.

INCOMPATIBILITY

A prescription should not contain such ingredients which can counteract one another either physically, or physiologically, when mixed together. If they do so, they are known as *incompatibles*.

Incompatibility, therefore, may be of the following kinds:—

I. *Physical*.—This is also known as *pharmaceutical*, and occurs when the ingredients are not soluble in water, so as to produce a clear solution; as oils, insoluble powders, some spirits, resinous tinctures, some extracts, etc., when ordered in a mixture. Oil when ordered in a mixture should be emulsified. Resins, resinous tinctures, insoluble powders, etc., require some suspending agents. Certain solids like menthol, camphor, chloral hydrate, thymol, phenazone and sodium bicarbonate when mixed form oily liquids.

II. *Chemical*.—Such drugs should not be prescribed as would chemically react on one another, unless such a reaction is desired. Chemical incompatibility can be classified under two heads:—

A. *Homogeneous*.—In this *no visible change of form*, such as the liberation of a gas or formation of a precipitate occurs, though the colour may be changed. Thus, acids and bases are chemically incompatible with each other; *e.g.* lactic acid with lime water. Again, if the resulting salt is soluble and poisonous, the chemical neutralisation cannot resist the toxic action, as hydrocyanic acid and alkalies, for KCN is as poisonous as HCN, although the alkaline carbonates are not incompatible with HCN.

B. *Heterogeneous*—In this there is a visible change of form, i.e. the production of a gas or a precipitate; CO_2 is the chief gas liberated in such a decomposition, sometimes H_2S . The precipitates or the insoluble compounds form the largest chemical incompatibles. This class can again be subdivided into:—

1. *Intentional*.—Seidlitz powder, black wash, all effervescing mixtures, ammoniated solution of quinine, etc., are examples of this variety. Vegetable astringents with chalybeates, and lead salts with solutions of opium also come under this category.

Unless the incompatibility in the prescription is intentional the dispenser should first consider whether the incompatibility is of such a nature as would endanger the life of the patient, when it should be referred to the prescriber; if it is not of such a nature the prescription should be dispensed as ordered adopting such method as will give as satisfactory a combination as can be expected under the circumstances.

2. *Avoidable*.—Sometimes however chemical changes occur by mutual combination of the different ingredients in a prescription with the formation of harmful or even dangerous compound. This form of chemical incompatibility is very difficult to master. A complete knowledge of chemistry and solubility of drugs can only help the student out of this difficulty. The following rule would greatly minimise his errors;—“*A drug should never be ordered in combination with any of its tests or antidotes.*” Thus, carbonates should not be given with free acids (except HCN); acid salts, basic salts, double citrates, e.g. scale preparations of iron, halogens, with solution of ammonia, etc.

Alkaloidal salts, with the exception of quinine sulphate, quinine tannate, quinidine sulphate, physostigmine salicylate, ergotoxine ethanesulphonate, emetine and bismuth iodide, and pelletierine tannate, are soluble in water, although the free alkaloids are only sparingly soluble. Therefore alkaloidal salts should not be prescribed with alkaline carbonates or hydroxides, e.g. liquor strychnine with aromatic spirit of ammonia, morphine salts with bicarbonates of sodium or potassium, as free alkaloids will be precipitated. Potassium iodide and tannic acid also throw down alkaloidal precipitates, specially if the solution is concentrated. Many fatal accidents have taken place from swallowing the last dose of a mixture containing a poisonous alkaloidal precipitate. Calcium and other metals of alkaline earth are precipitated by sulphates, phosphates and alkalies; salts of heavy metals are precipitated by alkalies, tannins, albumin and some alkaloids and acacia. Silver and lead are incompatible with chlorides, bromides and iodides; silver salts are also incompatible with organic substances. Most

metals are precipitated by tannic acid and substances containing tannin. Although, to some extent, the alkaloidal incompatibility can be avoided by the addition of HCl and alcohol yet it is a safer plan to follow the following practical rule, viz. "*All poisonous alkaloids as far as possible should be prescribed in simple solution, and not in too concentrated a state.*"

Sometimes explosive combinations result from inattention to grave incompatibility (*see below*).

III. **Physiological.**—When the pharmacological action of a drug is antagonised by that of another, both drugs are *physiological incompatibles* or *antagonists*. It is presumed that this antagonism takes place either in the blood or in the tissues. We do not know any drug which can fully and completely counteract the action of another on all points, though instances are common where *partial antagonism* takes place. Thus, opium contracts the pupils and depresses the respiratory centre, belladonna dilates the pupils and stimulates the respiratory centre (*see Opium and Belladonna*); hence both of them are partially physiological incompatibles to each other. Digitalis counteracts the action of aconitine on the heart; and strychnine and brucine that of bromides and chloral hydrate on the cord. The depressant action of aconitine on the heart is also neutralised by the stimulant action of atropine. Pilocarpine increases, while atropine decreases, both salivation and perspiration. (*see Antagonism, page 51*)

EXPLOSIVE COMBINATIONS

Certain drugs, such as chlorates, bichromates, iodates, nitrates, picrates, permanganates, oxide of silver, etc., are rich in *oxygen* or part with it very easily; while others, such as sulphides, iodine, reduced iron, hypophosphites, organic powders, charcoal, camphor, iodide of iron, ammonia salts, essential oils, etc., are *easily oxidisable*. An admixture between any two of these classes is sure to result in an explosive combination. The following are a few typical examples:—

1. A few tablets of potassium chlorate kept in a pocket with a box of safety matches caused explosion.
2. Potassium chlorate with tannic acid, catechu, morphine hydrochloride, or gallic acid mixed as a dry powder has been known to explode.
3. A mixture of liquor ferri perchloridi, glycerin and potassium chlorate explodes when warm.
4. Calcium hypophosphite alone, when triturated hard, sometimes causes explosion. Never heat it with glycerin.
5. Potassium permanganate should not be made into a pill with vegetable extracts or combined with glycerin.
6. Oil of turpentine and sulphuric acid, and amber oil and nitric acid are sure to explode violently.
7. Oxide or nitrate of silver with creosote forms a compound which may take fire if it becomes warm.
8. Chromic acid with glycerin, ether, strong alcohol, or organic substances causes an explosive combination.
9. Chloral hydrate and sp. ammon. aromat. in a mixture may liberate so much chloroform as to explode.

10. Bismuth subnitrate and sodium bicarbonate given in a mixture liberate CO_2 and may cause an explosion if the bottle is corked before allowing the gas to escape.

11. Tinct. iodine and solution of ammonia should not be prescribed together as iodide of nitrogen is formed, which causes explosion.

12. Erythrol tetranitrate is very sensitive to percussion. A young chemist lost his life from explosion due to the rubbing of the tetranitrate with milk-sugar in a mortar.

13. Chloride of lime triturated with sulphur causes explosion.

POISONOUS COMBINATIONS

1. Potassium chlorate and potassium iodide in solution do not react in ordinary temperatures but in the body produce a poisonous product, probably iodate of potassium.

2. Potassium chlorate given with syrup of ferrous iodide liberates free iodine in the stomach and causes severe gastric irritation.

3. Hydrocyanic acid dilute with metallic hydrates, carbonates, subnitrates, or subchlorides forms cyanides of metals which are more poisonous than the acid.

COMBINATION OF DRUGS

The main object of the prescriber should be to present his patient with an effective and rational prescription free from incompatibles. An admixture of several ill-understood and ill-chosen drugs can no longer be tolerated in these days of rational therapeutics. No drug should be ordered unless the prescriber is sure of the pharmacology of the drugs he is using. Simplicity in combination should be the rule, but it does not follow that one drug only is to be prescribed at a time. An effective combination of judiciously selected drugs is of great value in the treatment of disease. The following are the advantages of a good combination:—

1. *By a combination of various drugs, whose actions bear resemblance with one another, we can augment or intensify certain properties of a drug.*—Thus, a mixture of chloral hydrate and potassium bromide makes a better hypnotic than either given in large doses (see Synergism, page 51).

2. *By a careful admixture of corrigens, we can correct unpleasant and undesirable properties of a drug.*—Thus, ginger is added to Pulv. Rhei Co., Pulv. Jalap. Co., to remove griping. Hydrobromic acid lessens cinchonism.

3. *By a combination of two or more drugs, individually producing entirely different physiological effects, we can sometimes increase the potency of a remedy in a particular direction.*—Thus, by combining mercury with digitalis and squill, we can increase the diuretic properties of the latter drugs.

4. *By mixing such drugs as chemically decompose each other we at times get better results from the resulting products.*—Thus by giving potassium or sodium bicarbonate with citric acid, we get the benefit of carbonic acid gas and potassium or sodium citrate.

5. *By a combination of such substances as would assist the solubility or absorption of a drug, a more effective remedy can be obtained.*—Thus salicylic acid is almost insoluble in water, but it is rendered entirely soluble by the addition of borax, alkaline carbonates, hydroxides, etc. The absorption by the skin of the alkaloids of belladonna is greatly facilitated if belladonna is combined with fat, glycerin, oil or chloroform.

ART OF PRESCRIBING

WEIGHTS AND MEASURES IN A PRESCRIPTION

The weights and measures of capacity and length to be used in a prescription are those of the Metric System (see p. 9). The Imperial

system however is still used, and also the scruple, though rarely. Besides, certain signs indicating weights and measures of capacity are also common, which have not been officially recognised. They are:—

- Gr. = Granum, 1 grain = $\frac{1}{480}$ of a Troy ounce, or $\frac{1}{437.5}$ of an Avoirdupois ounce.
 ℥ = Scrupulum, 1 scruple = 20 grains.
 ℥ = Drachma, 1 drachm = 3 scruples or 60 grains or $\frac{1}{8}$ of a fluid ounce, or 60 minims.
 ℥ = Uncia, 1 ounce = 1 Troy ounce (480 grs.) or 1 fl. oz. (480 minims) or 437.5 grains of water.
 M. = Minimum, 1 minim = $\frac{1}{60}$ part of a drachm or the volume of 0.91145 grain of water.
 Gtt. = Gutta, 1 drop, supposed erroneously to represent 1 minim.
 O. = Octarius, 1 pint = 20 fluid ounces, or 1½ lbs. of water.
 C. = Congius, 1 gallon = 8 pints or 10 lbs. water.

As these symbols are apt to be misleading, the B.P. recommends that prescribers should cease to employ them. Solids should be prescribed in grains (gr.), when Imperial system is used, and ounces (oz. = 437.5 grs.); and liquids in minims (m.) and fluid ounces (fl. oz.). The quantities should be written in Arabic numerals. The symbol of gramme should be G. and for grain (gr.).

When 'drop' is used it should be measured by means of a tube which delivers in 20 drops 1 G. of distilled water at 15°C.

English Domestic Measures

- A tea-spoonful = 1 fluid drachm, or a little more
 A dessert-spoonful = 2 fluid drachms (about).
 A table-spoonful = 4 fluid drachms or ½ ounce (about)
 A wine glassful = 2 fluid ounces, or more.
 A gill = 4 fluid ounces, or more
 A tea-cupful = 7 fluid ounces, or more.
 A breakfast-cupful = 8 fluid ounces, or more
 A glassful = 12 fluid ounces, or more.
 A tumblerful = 15 to 20 fluid ounces.

These are only average measurements, for no cups or spoons are of the same size.

Indian Domestic Measures

MEASURES OF CAPACITY CURRENT IN THE BENGAL PRESIDENCY

- A Half-kancha = $\frac{1}{8}$ chattack or $\frac{1}{16}$ seer = 2 fl. drachms (about).
 A Kancha = $\frac{1}{4}$ ch or $\frac{1}{8}$ seer = 4 fl. drachms, or 218.75 grs. of distilled water.
 A Half-chattack = $\frac{1}{16}$ poa or $\frac{1}{32}$ seer = 1 fl. ounce (about)
 A Chattack = $\frac{1}{8}$ poa or $\frac{1}{16}$ seer = 2 fl. ounces (about)
 A Poa = $\frac{1}{4}$ seer = 8 fl. ounces (about)
 A Half-seer = $\frac{1}{2}$ seer = 16 fl. ounces (about).
 A Seer or 64 kancha, or 16 chattacks = 32 fl. ounces (about)

MEASURES OF CAPACITY CURRENT IN THE BOMBAY PRESIDENCY

- A Sundia-pallful = 1 drm.
 A Curd-pallful = 5 tollas or 2 ounces.
 A Swayapak-pallful = 10 tollas or 8 ounces.
 A Panchpatriful = 8 or 12 ounces.
 A lota or tambiaful = 3 or 4 lbs.

Indian Domestic Weights

1 Rupee or 1 tola	=	180 grains
$\frac{1}{2}$ " $\frac{1}{2}$ "	=	90 "
$\frac{1}{4}$ " $\frac{1}{4}$ "	=	45 "
1 Nickel 2 anna	=	90 "
1 " anna	=	60 "

PREScription WRITING

A prescription is **simple**, when it contains a basis and a vehicle or excipient with or without a corrective; and **complex** when it contains several adjuvants and corrigents besides the basis. The construction of a model prescription should be in the following order:—

1. The superscription, which consists of the symbol \mathcal{R} which originally symbolized the planet Jupiter, but now stands for *recipe* or take thou.

2. The inscription, or the body of a prescription, consisting of the names and quantity of drugs ordered, and contains the *basis*, or the chief ingredient; the *adjuvant*, to assist the action of the basis; the *corrigent*, to correct the injurious effects of other ingredients; and the *vehicle* or *excipient*, to give the prescription a suitable form.

3. The subscription, or the directions to the dispenser, such as *misce, fiat, mist., pilula, etc.*

4. The signature (from *L. Signature*—let it be labelled) or the directions to the patient. This is written either in English or in vernacular.

5. The Prescriber's name or initial and the date. These are put at the bottom. The patient's name should be written at the top of the *recipe*.

The following is an example:—

Patient's name:

Superscription:	\mathcal{R}	
Inscription:	{	Quinina Sulphas, gr 10 (<i>basis</i>) Acid. Hydrobrom. dil, ms. 10 (<i>adjuvant</i>). Syrupus Limonis, ms. 60 (<i>corrigent</i>) Aqua Chloroformi, ad fl. oz. 1 (<i>vehicle</i>).
Subscription:	{	Fiat mistura, Misce Mitte talis six.
Signature:		One ounce thrice a day.
Date:—		<i>Prescriber's Name —</i>

It will be observed that quinine is given with the object of checking malaria, and as the sulphate is insoluble in water, Acid. Hydrobromicum Dil. is used to dissolve it, and also to prevent cinchonism. Chloroform water is used as a diluent and to make the dose a measurable quantity. A vehicle may be of no medicinal value, e.g. plain water, or only used to give flavour. Sometimes it has a medicinal value, as when infusions are used. "ad" fl.oz. 1 means that after all the ingredients have been measured the vehicle should be added to make the total quantity one ounce.

In the above prescription the quantities have been given for a single dose, and the dispenser is asked to supply six doses. Sometimes, however, instead of depending on the dispenser to calculate the total quantities of each ingredient, the physician makes the mental calculation for the whole amount contained in the prescription.

The above prescription in this case takes the following form:—

Patient's name

Superscription:	\mathcal{R}	
Inscription:	{	Quinin Sulph. gr 60 (<i>Basis</i>) Acid Hydrobrom. Dil. ms. 60 (<i>Adjuvant</i>) Syr. Limon ms. 360 (<i>Corrigent</i>) Aqua Chloroformi ad fl. oz 6 (<i>Vehicle</i>)
Subscription:	{	Fiat mistura, Misce Put six marks
Signature:		One mark three times a day.

Date.

Prescriber's name

Every prescription should be written with a definite object. The prescriber therefore should weigh each drug carefully before writing.

Let us take another example. Supposing we wish to write a sleeping draught for an adult, we first of all think what hypnotic will suit our patient, and decide on chloral hydrate and write accordingly

R̄

Chloral Hydras, which forms the *basis*

Then we argue that another preparation like potassium bromide will help in its action and will act as an *adjuvant*, we therefore write as

R̄

Chloral Hydras

Potassii Bromidum

We now consider an agreeable corrective and vehicle which would give it a flavour, and therefore add further

Syrupus Aurantii

Aqua Anethi Dest

Having written so far we consider the dose. Here we must be guided by the object for which the prescription is given, and whether the patient should take only one dose or more than one. We order for two doses in case the first dose does not produce the desired effect. The dose of chloral hydrate is 5 to 20 grs., and of potassium bromide is 5 to 30 grs. We make a mental calculation and decide on giving 15 grs. of each, and for two doses we order grs. 30 of each. Now we add 60 ms. of syrup for each dose and sufficient vehicle to make up the total bulk to 2 ozs. Then we proceed to write directions to the dispenser, *i.e.* to mix and make a draught, *viz*—M. ft. Haust., and the final direction—*Sig.*—one ounce at bed time to be repeated after two hours if necessary.

The complete prescription will now take the following form:—

Patients name —

R̄

Chloral Hydras

Pot. Brom. }

... aa grs. 30

Syr Aurant

... ms. 120

Aqua Aneth Dest

. ad. fl. oz. 2

M ft. Haust.

Sig.—One ounce at bed time to be repeated if necessary after two hours

Date :

Prescriber's name

Sometimes a prescription is written in bulk and the patient is directed to take a required amount from it, thus:—

R̄

Sod. Sulph.

.. grs 120

Mag. Sulph.

.. grs. 240

Sod. Bicarb

... grs 120

Mag Carb.

... grs. 60

M ft. Powder

Sig.—Two teaspoonfuls in half a tumbler of water every morning.

Date

Prescriber's name

In writing prescriptions the following points should be observed:—

1. Always begin each line with a capital letter.
2. It is better to write the names of the active ingredients first, and then of corrective, etc., and vehicle or excipient last.
3. Use Latin names for the ingredients and for the directions to the dispenser. The directions to the patient may be given in commonly used Latin; but the dispenser must write the directions on the label either in English or in the vernacular of the place.

4. When in doubt always write in plain English. It is most important that the dispenser should understand the meaning of expressions used in the prescription.

5. Never hand over the prescription without reading it over again.

ELEGANT PRESCRIPTIONS

Elegance in a prescription should always be aimed at, but it does not follow that the student should prescribe only fancy pills, capsules, tablets and cachets. These are good and useful, but they cannot supply the place of a mixture. The importance of giving a mixture in an inviting and palatable form cannot be over-estimated. We have various flavouring agents. Aromatic syrup, syrups of orange, glucose, lemon, Virginian prune, tolu and ginger are the popular ones. During the hot months, mixtures containing syrups soon decompose, but glycerin and flavouring waters may be substituted for them. Spirit of chloroform, chloroform water and liquid extract of liquorice cover the taste of many bitter and saline mixtures. Syrup of yerba santa disguises fairly well the taste of quinine salts. Rose water, orange-flower water, cinnamon water and anise water are good flavouring vehicles either for mixtures or for lotions. Cinnamon water disguises the odour of castor oil. Syrups of rose and red poppy are only used as colouring agents. Compound tinctures of lavender and cardamoms are used both for flavouring and for colouring purposes. Liniments or ointments can be perfumed by otto of roses, oil of neroli and lavender. Nauseous and bitter powders can be given in cachets or pills, the pills can be coated or gilded.

DIRECTIONS TO THE PATIENT

Make it a point to give directions in a definite manner. They should be short, simple and to the point. It is very important to mention the hour of the day when medicines are to be administered. To the student this may appear confusing in the beginning, but the following hints will aid him in this direction :—

1. Mineral acids, as a rule, are given after meals.
2. Alkalies when used to neutralise acid secretion should be given after food, and when prescribed as a systemic alkaliser should be given between meals.
3. Gastric sedatives, such as dilute hydrocyanic acid, bismuth salts, are best given on empty stomach, as we want their local action.
4. Pepsin, papain, taka-diastase should be given immediately after or along with meals.
5. Dilute hydrochloric acid when prescribed to help intestinal digestion should be given one to two hours after food, so also pancreatin and other pancreatic ferments.
6. Cod-liver oil and its preparations should be administered after and not before food. If given before they spoil the appetite.
7. All preparations of iron, specially the astringent varieties, are to be administered after meals.
8. All stomachics and bitter tonics, such as calumba, chiretta, quassia, are given quarter to half an hour before food.
9. Arsenic is always given after meals, except in a few rare cases, when its local action on the stomach is desired.
10. Potassium permanganate is always given after food.
11. Purgatives should be given either at bed time or early in the morning depending upon the rapidity of their action. Castor oil and salines are best given early in the morning as they take only a few hours to act. The more slowly acting ones, e.g. bed pills containing aloes, etc., should be given before retiring at night.
12. Emmenagogues should be taken at least one week before menstruation.

13. All diaphoretics act well when the patient is kept warm, and diuretics when cool.

14. Hypnotics, as a rule, should be taken at least half an hour before going to bed; but sulphonal two or three hours before, as it dissolves slowly.

15. Morphine should be administered subcutaneously when the patient is in bed.

16. Bromides, when given as a sedative, are to be administered after meals or at bedtime.

PREScription FOR CHILDREN

Great tact and caution are required in prescribing for children. The hints given below will greatly help the student in this direction:—

1. The dosage must be in proportion to the age.

2. The bulk of a mixture must be small, not exceeding one or at the most two tea-spoonfuls.

3. Medicines must be made as palatable as possible. Children like either sweet or tasteless medicines. They refuse bitters. Quinine ethyl carbonate (euquinine) or aristochin may be used as tasteless substitutes for quinine salts. Quinine should not be dissolved in mineral acids, as its bitterness is intensified.

4. Infants do not refuse either castor oil or cod-liver oil, but older children often reject the former. Cod-liver oil with extract of malt is never refused.

5. Do not order pills for children, give dry drugs in the form of powders mixed with honey, syrup, milk, sweetened water, malt extract, or jam.

6. Children bear belladonna and hyoscyamus in fairly large doses.

7. Arsenic, too, is well borne, some choreic children can take very large doses without harm.

8. A tea-spoonful of castor oil to a new-born babe is not a big dose.

9. Children are *very susceptible to opium*. Opium and its preparations should therefore be used with caution in children's practice*.

10. Plain dill or anise waters make good all-round general vehicles for children's mixtures.

11. For round worm, santalin must be given on an empty stomach at night and then followed by a dose of Gregory's powder next morning. It is best given with calomel and sugar followed by a saline if necessary.

12. Children tolerate calomel better than adults and are rarely salivated.

13. Expectorants are best given in the form of syrups or mixed with a syrup.

*In some part of India infants are habituated to the use of opium. It is given with a view to keep them quiet while their mothers are at work. Many wet-nurses secretly administer it to their wards. The writer has seen an infant only 14 months old taking daily one grain of opium, without any other evil effects than constipation.

PART III

PHARMACOLOGY AND THERAPEUTICS

HOW DRUGS ACT

By the action of a drug on the human organism is understood the interaction between a drug and the blood and the tissues, whereby either the existing functions are altered, or certain functions are brought more into prominence which were latent before. Thus, the functions may be increased or diminished, and the drug is then said to *stimulate* or *depress* as the case may be. Sometimes this stimulation has an injurious effect on the tissues and it is then known as *irritation*. A moderate degree of stimulation continued for a long time leads to fatigue or exhaustion of the organs concerned.

Some drugs act more powerfully on certain organs and tissues than others, and this preferential effect is known as the *selective action of the drug*. This fact has been taken advantage of in the modern treatment of parasitic diseases and forms the basis of chemotherapy. Substances have been discovered which are supposed to be harmful to the infecting parasites, *i.e. parasitotropic*, and at the same time harmless to the host, *i.e. not organotropic*. The conception of chemotherapy is, however at its best, a speculation, and most of the parasitotropic agents act not so much by their selective affinity for the parasite but by definite pharmacological action on the cells of the body of the host.

A drug may affect the body *directly*, *i.e.* when it comes in contact with a particular organ and produces its effects on that organ. The direct action of cantharidin on the skin is irritation. This action is also known as the *local action*. Many drugs, after absorption, produce changes on other organs of the body and this action is then known as the *systemic effect*. The action of digitalis on the circulation or kidneys is the systemic effect of the drug after absorption. This is also called *indirect* or *remote action* of the drug. Thus the immediate local action of aconite on the tongue is tingling and numbness, and its indirect or remote action on the heart is slowing of beat due to stimulation of the vagal centre.

By *primary action* is meant the effect that a drug produces in its unaltered state. When a drug forms a different compound in the body which produces the physiological effects, it is known as the *secondary action* of the drug. Hexamine when excreted with the urine acts as an antiseptic by being converted into formaldehyde.

It is not always very easy to explain exactly how the different drugs produce their pharmacological effects on the system. Although many attempts have been made to explain how the different drugs produce their effects, still we are far from any satisfactory solution as to the real nature of the action of most of them. Since the processes of life are governed by the chemical and physical changes in the constituents of the cells, it is possible that the different drugs may act by altering or modifying these chemical and physical factors in the cells by entering into definite chemical combination with the constituents of the protoplasm and produce corresponding changes in their function. An attempt was therefore made to explain the action as being due to *chemical changes*. Although the effects produced by some drugs are due to these changes, yet the action of many is produced differently and cannot be explained by chemical theory alone. It will be seen, when discussing drugs acting on the autonomic nervous system, that drugs while stimulating the different nerve endings act by liberating chemical substances which transform a nervous stimulus into a chemical reaction; for instance, stimulation of parasympathetic acts by production of *acetyl choline* and that of sympathetic by the formation of *adrenaline-like* substance. Some drugs act in a purely *mechanical* way, while others affect the various cells of the body by altering the *surface tension* resulting in osmosis, and modify the particular function of the cells. Mayer and Overton explain the action of another group of drugs, *viz.* the narcotics, as being due to their solubility in lipoids. They argue that in order that a drug may produce any physiological effect it must first get into the cell, and other things being equal, one would expect a quicker and more powerful effect from a lipoid soluble substance than from one that is not thus soluble. While discussing narcotics it will be seen that there are many objections to this theory, and that the action of all narcotics cannot be explained on the theory of lipoid solubility. Yet another school holds that it is not the solubility of a particular drug in the cell that determines the action, but the activity depends upon the adsorptive power owing to the colloidal nature of the cell protoplasm. This is how the bactericidal action of mercury (*see Mercury*), and adsorption of toxins by kaolin are explained.

THE CHEMICAL COMPOSITION AND CONSTITUTION AND THE PHYSIOLOGICAL ACTION OF A DRUG

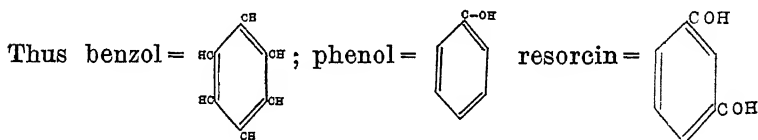
Recent works have demonstrated that the physiological action of a drug very often depends upon its chemical constitution as will be evident from the following:—

(a) *The molecular arrangement in a compound sometimes*

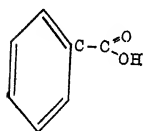
determines the action of a drug. Thus isomerides have the same chemical composition and the same percentage of weight, but differ in properties, on account of their different molecular arrangements. Resorcin and pyrocatechin are isomers $C_6H_4(OH)_2$. The former is sweet, the latter is bitter.

(b) *It is possible to modify the physiological action of a drug by artificially modifying its chemical constitution.* Fraser, Crum Brown and others have shown that by introducing a methyl radicle into the molecules of strychnine, brucine and thebaine, new compounds are formed, which instead of acting as convulsants, are paralyzers of the peripheral terminations of the motor nerves.

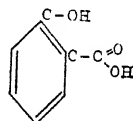
Similarly benzol, C_6H_6 , the mother substance of the coal-tar series has a low toxicity, because it cannot react with protoplasm. It becomes toxic by replacing part of the H atoms with other groups, specially by OH forming phenol, or by CO_2H , or by both. The OH radicle is the most active; the antiseptic and toxic action increasing with the number of OH group.



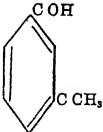
The introduction of CO_2H group alone, *i.e.* benzoic acid does not render the substance more active. But both OH and CO_2H , *i.e.* salicylic acid, results in a compound which is less toxic and less antiseptic than phenol but has a peculiar antirheumatic property.



Benzoic Acid



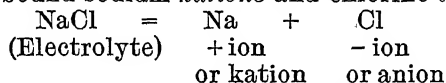
Salicylic Acid

The substitution of an H of C_6H_5 in phenols by alkyls=cresol,  leads to an increase of the antiseptic power, and diminishes at the same time the toxicity to tissues.

THE ACTION OF A DRUG AND ITS POWER OF DISSOCIATION INTO IONS

When we consider the action of a powerful drug like strychnine, we find that its various salts produce the same effect which the acid radicle (sulphate, nitrate, etc.) does not modify. This is not however the case with less powerful bodies, *e.g.* sodium; here the acid radicle with which it is combined greatly modifies its action, as is observed in the different effects resulting from the administration of NaCl

and Na_2SO_4 . To appreciate these differences of action it is essential to understand the *ionic theory*. All substances are divided into two groups, *electrolytes* and *non-electrolytes*. An electrolyte is a substance which is capable of being decomposed by the electric current, as sodium chloride, potassium bromide, etc. The theory assumes that certain substances such as inorganic acids, salts and bases in solutions undergo partial decomposition into their constituent elements or radicles called *ions*. These ions carry definite charges of electricity. Thus, sodium chloride, if dissolved in water, exists in part commingled, but not chemically bound sodium *kations* and chlorine *anions*.



A non-electrolyte is a substance which cannot be further decomposed without losing its chemical identity. In ionic dissociation when the solvent is evaporated the salt is obtained in the same state as before solution; in chemical decomposition however the evaporation of the solvent will not re-unite the separate ingredients.

The importance of this theory to pharmacology is that it is the ions of the salts and not the whole molecule which give rise to pharmacological action. For instance, when an ionisable substance is introduced into the blood it has a threefold effect on the functions of the body, *viz.*—

- (a) That due to the influence of its kation,
- (b) that due to the influence of its anion, and
- (c) pure salt action.

Sometimes the basic and sometimes the acid ion produces the chief effect, and when neither ions are potent we get the typical salt action. When the two ions are of approximately the same potency we have the combined effects of both ions. The following examples will serve to illustrate:—

NaCl = typical salt action.

Na_2SO_4 = action of acid ion predominates, and acts as a purgative.

FeSO_4 = astringent and hæmatinic, action of basic ion predominates.

MgSO_4 = action of both ions predominates, therefore although the sulphate ion is common with Na_2SO_4 , it acts as a more powerful purgative because of the Mg-ion.

Drugs that are not dissociated in the tissues act as molecules and not as ions. This important factor should be remembered to avoid confusion. Thus potassium cyanide is a poison because CN-ion is dissociable, while in potassium ferrocyanide the CN-ion is not dissociable and therefore this salt is not a poison. Again inorganic arsenic compounds are poisonous, whereas cacodylic acid has not the same toxicity because it does not ionise.

It follows therefore that the action of certain drugs depends not only on the amount of dissociation which they undergo but also on the relative absorptive power of the dissociated ions and on the rate of excretion. Scale preparations of iron which do not dissociate are not astringents and do not impair digestion. Mg-ion being absorbed with difficulty and excreted rapidly, its effects are not observed when administered by the mouth, although given parenterally it has a profound depressing effect on the central nervous system. The disinfecting power of mercurials varies with the amount of dissociation which the different salts undergo and not on the quantity of mercury in solution. Finally, potassium salts given by the mouth produce no toxic effect because their rate of excretion exceeds that of absorption.

THE REACTION OF BODY TISSUES AND BODY FLUIDS AND THE ACTION OF DRUGS

By the term reaction of a solution is meant the degree of acidity or alkalinity. The acidity and alkalinity of tissues depend upon the dissociation of H and OH ions, and the degree of acidity of any solution depends upon the relative amounts of free hydrogen ions (H) and free hydroxyl ions (OH) which it contains. When both ions are balanced the solution is neutral. These two ions part readily with their electric charges and produce marked alterations in the functions of cells. Chemically pure water is neutral and when it dissociates it yields equal amounts of H and OH ions. At 22°C. 10,000,000 litres of pure water contains 1 grm. of H and 1 grm. equivalent of OH ions. The concentration of hydrogen ions (cH) is therefore 10^{-7} , and the concentration of hydroxyl ions (cOH) is 10^{-7} .

Such negative figures are difficult to deal with in practice, and therefore the potential of H-ion concentration is taken as the standard, rather than the actual H-ion concentration itself. The hydrogen-ion-concentration-potential or *pH* is the decimal logarithm of the reciprocal of cH, and in the case of water, *pH*=7.0, and a standard of *pH*=7 may be taken as neutral.

The normal reactions of the tissues and fluids within the body proper are normally neutral, inclining a trifle towards alkalinity, *i.e.* *pH*=about 7.1 to 7.8; the gastric juice and the urine in higher animals are the only exceptions. The *pH* of gastric juice is 0.9 to 1.6; urine, 6.0; cow's milk, 6.7; human milk, 7.1; saliva, 6.9; pancreatic juice, 8.3; etc. Living cells are dependent upon the maintenance of a strictly limited H-ion concentration in their environment for the normal performance of their functions.

The normal blood has a *pH* range of from 7.3 to 7.5; and life is incompatible when the *pH* of blood is below 7.0 or above 7.8. While the *pH* of different excretions varies

between wide limits, the maintenance of the pH at its normal level in the blood and tissues is very important. This is regulated by a fine adjustment of different mechanisms (see Acidosis and Alkalosis). The carbonates and the alkaline phosphates of the blood and tissues form the alkaline reserve, while the carbonic acid and acid phosphates, the acid reserve. These act as "buffers" and tend to neutralise any attempt to change the actual reaction.

The importance of the knowledge of pH of the different tissues of the body to the pharmacologist is great. Action of drugs which are supposed to have a selective affinity for certain organs or tissues often depends upon their pH reaction. Thus Acton has shown that at pH of 8, quinine kills paramœcium at a dilution of 1 in 10,000; while a concentration of 1 in 100,000 is necessary at pH of 7. Dale has shown that emetine in large doses failed to cure dysentery, in kittens, produced by strains from man, while these men were cured by a course of emetine. It is possible that the pH of the human gut is responsible for the effect of emetine. In fact emetine acts ten times more powerfully, if the acidity of the gut, which has a pH of about 6.2 in amœbic dysentery be reduced or rendered alkaline to a pH of 8. It is therefore argued that besides the drug and the infective organism (*E. histolytica*) other factors have to be considered in the cure of amœbic dysentery, and this missing factor is supplied by the host as the result of interaction between emetine and tissues. It has been found that a dilution of emetine hydrochloride 1 in 5,000,000 is lethal to *E. histolytica* *in vitro* within four days with a pH of 6.4, while its potency is considerably reduced with a greater acidity. Mercurial diuretics act better when partial acidosis is produced by the use of ammonium chloride. Similarly production of acidosis helps absorption of ionisable calcium. It is clear, therefore, that the action of drugs in certain instances is modified or intensified by the pH of the particular organ over which they produce the main effect.

GROUP I

THE ALKALIES AND METALS OF ALKALINE EARTH

Potassium, Sodium, Ammonium, Lithium, Calcium,
Magnesium, Barium

Before discussing the action of the individual drugs of this group we had better consider their therapeutic uses from a broad point of view. Certain salts of the alkalies—potassium, sodium, ammonium and lithium, and some of the salts of the alkaline earths—magnesium and calcium, are employed therapeutically as *antacids*. The salts of the

former, being rapidly absorbed from the alimentary canal. manifest after a local action in the stomach, certain systemic action, whereas the salts of the latter are absorbed with difficulty and exhibit an active action on the intestinal tract, magnesium being laxative, calcium constipating. Some of the alkaline salts are strong caustics, while others are mild antacids. The former are chiefly the hydroxides of potassium and sodium, and the oxide of calcium. These act by dissolving albumin, extracting water and saponifying fats; while the others, *viz.*, the carbonates and bicarbonates of potassium, sodium, and lithium, and the carbonates and oxides of magnesium and carbonate of calcium act merely as antacids. Some are not locally antacids, but are converted into carbonates in the blood and tissues and thus increase the alkalinity of the blood, and are therefore systemic alkalisers. They are the acetates, citrates and tartrates of sodium and potassium.

Barium, though it belongs to the group of metals of the alkaline earth, has none of its properties common with calcium and magnesium, except that it is absorbed with difficulty by the epithelial cells.

Antacids are therefore of two types :

1. *Those of alkaline reaction*, *viz.* (a) the caustic alkalies ; and (b) the milder alkalies, the bicarbonates and carbonates.
2. *Those not of alkaline reaction*, *viz.* acetates and citrates.

P TASSIU

Potassium salts are present in large quantity in both animal and vegetable foods, and although they are absorbed in large amounts very little ill effects are observed. In fact about 2 to 3 ounces are daily ingested with the vegetable food without any specific action of potassium ion being elicited, because the salts diffuse very rapidly through the cells and are excreted very quickly. It is only when the salt is given intravenously or subcutaneously that the specific effects of potassium ion are observed. These are characterised by depression of the central nervous system, heart and other muscles. When used therapeutically potassium salts produce the effects through the acid radicles and are practically equivalent to the corresponding sodium salts. The systemic effect of potassium when administered by the mouth is only possible if the dose is very large and the mucous membrane of the intestine is corroded and its excretion is checked by ligation of the kidney vessels.

In frogs the muscular movements become first weak and then abolished. In mammals the effects are characterised by muscular weakness and apathy with rapid and laboured respiration from anæmia of the centre.

It is a powerful depressant to the heart, which becomes slow and weak. The systole becomes weaker and the heart

of a frog stops in diastole. Injected intravenously it causes a rapid fall of blood pressure and slowing of the heart, accompanied by dilatation and heart block. These effects are due to the direct action of the drug on the heart muscle and

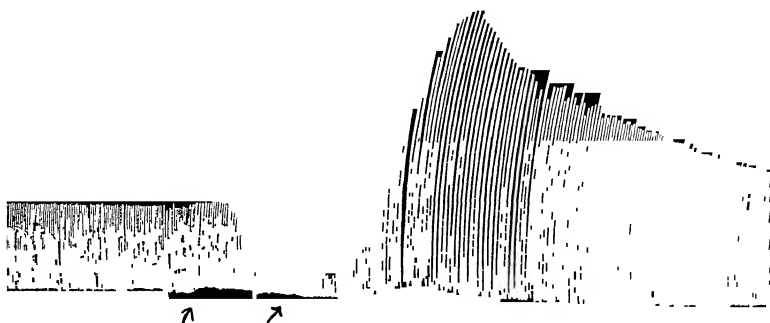


FIG. 1.—ANTAGONISM OF CALCIUM TO POTASSIUM

Isolated rabbit's heart perfused with oxygenated Ringer's solution. At the point of 1st arrow a small dose of potassium chloride was added to the Ringer showing depressant effect of potassium on the heart. At 2nd arrow calcium chloride was added. Note the effect on the heart.

not to any effect on the vagus mechanism. When injected into an artery instead of into a vein it causes a sudden rise of blood pressure from peripheral vaso-constriction due to its direct action on the muscles of the vessels.

The same depressant effect is observed on the voluntary muscles. It diminishes the height of contraction, lengthens the latent period and decreases the conductivity and excitability. This effect is antagonised by calcium, barium and veratrine. On the plain muscle it diminishes the automatic movement throughout the body.

POTASSII HYDROXIDI

Potassium Hydroxide. (Pot. Hydrox.). KOH

Syn.—Caustic Potash; Potassa Caustica

Source.—Obtained by the electrolysis of an aqueous solution of potassium chloride. It contains not less than 85 p.c. pure potassium hydroxide and not more than 4 p.c. K_2CO_3 .

Characters.—Deliquescent, corrosive, alkaline, white sticks, or fused masses. *Solubility*.—In 0.95 part of water, and in 3 parts of alcohol (90 p.c.).

Incompatibles.—Acids, heavy metals, alkaloids.

OFFICIAL PREPARATION

1. *Liquor Potassii Hydroxidi*. Syn.—*Liquor Potassæ*.—5 gms. of potassium hydroxide in 100 mls of water. A colourless, odourless, strongly alkaline liquid, with sp. gr. 1.045. *Impurities*.—Carbonates, sulphates, chlorides and other metals.

NON-OFFICIAL PREPARATION

1 Pasta Potassæ et Calcis. *Syn*—*Vienna Paste*—Caustic potash and quicklime in equal weights. Add alcohol or glycerin *q s* to form a paste

S O D I U M

Sodium Hydroxide. (Sod. Hydrox.). NaOH

Source.—Obtained by the electrolysis of an aqueous solution of sodium chloride. Contains not less than 95 p.c. of sodium hydroxide

Characters.—White sticks, fused masses or scales; dry, hard, brittle, showing crystalline fracture. Deliquescent; strongly alkaline and corrosive. Rapidly absorbs CO_2 . *Soluble* in 1 part of water, freely in alcohol (90 p.c.).

P O T A S S I U M

Potassium Bicarbonate. (Pot. Bicarb.). KHCO_3

Source.—Obtained by saturating a strong aqueous solution of potassium carbonate with carbon dioxide. Contains not less than 99 p.c. of pure potassium bicarbonate.

Characters.—Colourless, transparent, monoclinic prisms, or white granular powder. Taste, saline, feebly alkaline. *Solubility.*—1 in 4 of water. Almost insoluble in alcohol (90 p.c.).

Incompatibles.—Acid substances, alkaloids and magnesium sulphate.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

N.B.—20 parts by weight are neutralised by 14 parts of citric and 15 of tartaric acid.

P O T A S S I U M

Potassium Carbonate. (Pot Carb.). K_2CO_3

Syn—Salt of Tartar

Source.—Obtained by the interaction of potassium sulphate and calcium carbonate. Contains not less than 99 p.c. of pure potassium carbonate.

Characters.—A white, crystalline powder. Taste, strongly alkaline. *Solubility.*—1 in 1 of water Insoluble in alcohol (90 p.c.).

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 gm.

S O D I U M

Sodium Bicarbonate. (Sod. Bicarb.). NaHCO_3

Source.—May be obtained by the interaction of sodium chloride and ammonium bicarbonate. Contains not less than 99 p.c. of sodium bicarbonate.

Characters.—A white powder, or small, opaque, monoclinic crystals, with saline taste. Slightly alkaline. *Soluble* in 11 parts of water. *Twenty grammes neutralise 16.7 grammes of citric acid, or 17.8 grammes of tartaric acid.*

Incompatibles.—Acids and acid salts, *e.g.* bismuth subnitrate, heavy metals, alkaloidal salts.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

S O D I U M

Sodium Carbonate. (Sod. Carb.). $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$

Syn.—Soda or Washing Soda.

Source.—Obtained by action of heat on sodium bicarbonate, and subsequent crystallisation from water. Contains not less than 99 p.c. of pure sodium carbonate.

Characters.—Transparent, colourless, rhombic crystals. Efflorescent. Taste, strongly alkaline; odourless. *Soluble* in 2 parts of cold

water. *Twenty grammes neutralise 9.8 grms. of citric acid, or 10.5 grms. of tartaric acid.*

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

SO D I A C A R B O N A T E E X S I C C A T U S

Exsiccated Sodium Carbonate. (Sod. Carb. Exsic.)

Syn.—Sodii Carbonas Monohydratus, U.S.P.

Source.—Obtained by action of heat on sodium bicarbonate. Contains not less than 99.5 p.c. of pure anhydrous sodium carbonate

Characters.—A dry, white powder; odourless. Taste, strongly alkaline. Readily soluble in water.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

PHARMACOLOGY OF CAUSTIC POTASH, CAUSTIC SODA, - CARBONATES AND BICARBONATES OF POTASSIUM AND SODIUM

Externally.—Applied to the skin a concentrated solution of caustic potash or caustic soda acts as a powerful irritant and caustic. It has a strong affinity for water and dissolves albumin. The solutions of carbonates are less caustic than the hydroxides. A weak solution of caustic potash or a solution of carbonate will soften the skin, dissolve the oily secretions of the glands and cleanse the surface more thoroughly than plain water. Applied for some time they penetrate deeply and cause irritation and redness. Caustic potash and caustic soda are therefore rubefacient, antacid and detergent.

Internally. Gastro-intestinal tract.—The hydroxides and the carbonates have an alkaline taste and dissolve the superficial layers of the lining membrane and the mucous secretions in the mouth. Concentrated solutions may cause deep erosions as on the skin, while very dilute solutions only excite a reflex flow of saliva. In the stomach the hydroxides and the carbonates exert the same corroding effect when given in concentrated solutions; in dilute solutions they are mild irritants and may cause gastritis. The bicarbonates produce no such effect on the stomach. They dissolve mucus and neutralise acid, but their effect like all alkalies will vary greatly according to the nature of the stomach contents at the time of administration. Given during the digestive period they have the following definite effects, *viz.*—

- (a) reduce the gastric secretion,
- (b) neutralise some of the hydrochloric acid,
- (c) liberate CO₂ gas, which acts as a carminative; and
- (d) inhibit gastric movement and delay the opening of the pyloric sphincter.

The effect on gastric secretion is not quite clear. It is claimed that given during digestion they only diminish acidity temporarily, followed by a rise above normal. Indeed some hold that while alkalies inhibit gastric secretion when

given before meals, they increase the secretion when administered during the meals. This is possibly due to the liberation of CO_2 , for Pawlow observed that gastric secretion was increased by the presence of CO_2 . Dilute solutions act as mild irritants to the stomach walls and thus improve the circulation, help expulsion of gas, and reduce pain and distension much in the same way as any other mild irritants like volatile oils.

In cases of fermentation, by neutralising the organic acids which tend to cause pyloric spasm, they relieve that condition.

In the intestine the alkalies by neutralising or diminishing the acidity of the gastric contents have a retarding influence on the pancreatic secretion, which is normally stimulated by the passage of a highly acid fluid from the stomach, although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted. In hyperacidity, however, the alkalies render the contents of the intestine less irritating and thus have a tendency to allay catarrh. Stadelmann has shown that alkalies have no effect on the secretion of bile, and are not excreted in it, and do not cause any change in its reaction. Very large single doses cause vomiting. Repeated large doses open the bowels; the bicarbonate of soda sometimes acting as a purgative.

Blood.—All these salts are freely absorbed and rapidly excreted. They are neutralised by the CO_2 in the tissues and circulate as neutral bicarbonates. The reaction of the blood remains unchanged, but the alkali available for the neutralisation of acid is augmented. If given for any length of time, they cause the quality of the blood to deteriorate and reduce the body weight.

Alkalies increase oxidation *in vitro*, and for this reason they have been credited with an action on metabolism. But they do not increase the alkalinity of the tissues to any large extent and are very soon excreted by the urine. The estimation of nitrogen metabolism has yielded different results. Similarly they are supposed to favour oxidation of fats and proteins causing an increased consumption of oxygen and excretion of carbonic acid. The question of oxidation of tissues has also received much attention by different investigators, but the results were contradictory. In fact tissue waste is not increased by alkalies.

Heart and circulation —It has been thought that potassium salts are muscular depressants and therefore tend to slow and weaken the heart. But in therapeutic doses given by the mouth these salts are non-depressant and inert. In this country (India), where a vegetable diet is widely used, very large quantity ($1\frac{1}{2}$ to 3 oz.) of potassium salts is ingested daily without any such effect; and, as pointed out

by Dixon, they are excreted so rapidly that we get no specific action. In practical therapeutics potassium salts may be regarded as equivalent to the corresponding sodium ones, except when they are given by injection.

Respiratory tract.—These salts stimulate the bronchial secretion, and make the mucus less viscid. They are therefore **expectorants**. Potassium iodide possesses this property in a very marked degree.

Kidneys, etc.—Both the bicarbonates and the carbonates as well as the vegetable potash salts, are eliminated as carbonates, and in this way they stimulate the secretion of urine, and are therefore **diuretics**. They also **alkalise** the urine and thereby increase its capacity of holding more **uric acid in solution**. Passing over the mucous membrane of the genito-urinary tract, they either exercise a direct sedative action on it, or by rendering the urine alkaline soothe any irritation that may be present.

Toxic doses of alkalies, or when continued in large doses, cause alkalosis giving rise to headache, vomiting, general prostration, and possibly tetany due to diminished calcium in the plasma.

TOXICOLOGY OF THE CAUSTIC ALKALIES

Persons are not often poisoned by the caustic alkalies, but accidents occasionally happen through their swallowing by mistake either *pearlash*, which is a mixture of potassium carbonate and potash, or *soap-lees*, which contains the corresponding sodium salts.

The symptoms are a caustic taste in the mouth and burning heat in the throat, the mucous membrane of which becomes swollen, soft and red. This is followed by pain in the stomach, vomiting, sometimes of blood, diarrhoea, feeble pulse, general collapse from shock. On post-mortem examination, the whole mucous membrane from the mouth to the stomach is found red, swollen and excoriated.

Recently several cases of poisoning by caustic soda were recorded by Willimott and Gosden* from Cyprus, most of which were suicidal. The symptoms were burning pain in the mouth, throat and stomach with exhaustion and shock. Some had vomiting of blood, perforation of the œsophagus and stomach. If recovery occurred there was stricture of the œsophagus and pylorus. Post mortem showed necrosis of the liver and kidneys.

Treatment.—Any rapidly acting emetic, or a hypodermic injection of apomorphine. If no emetics are available, give copious draughts of warm water and tickle back of throat with a feather. After vomiting has occurred give (1) feeble acids (e.g. vinegar, lime-juice, dilute acetic acid or citric acid); (2) demulcents (oil, linseed tea, white of egg).

N.B.—Do not wash out the stomach with the stomach-pump as there is danger of damaging the softened mucous membrane.

THERAPEUTICS OF CAUSTIC POTASH, CAUSTIC SODA, CARBONATES AND BICARBONATES OF SODIUM AND POTASSIUM

Externally.—Caustic potash in the form of the solid stick is occasionally applied to remove growths such as warts, or to destroy lupus. Being very deliquescent its action

* *British Medical Journal*, June 9, 1934.

spreads to the surrounding and deeper tissues and it is necessary to protect the tissues by applying blotting paper to absorb moisture. Acetic acid or vinegar diluted should be applied to neutralise the caustic when further action is not required. As it has been found that it often caused severe caustic action, the application of **Vienna Paste** has been recommended as its action is milder and is more manageable. Cotton wool soaked in liquor potassæ and applied over an ingrowing toe-nail makes it soft enough to be peeled off easily. A solution of the bicarbonate (60 grs. to 1 pt.) allays itching of many skin diseases, and is used as a soothing lotion in dermatitis, urticaria, etc. A weaker lotion softens the crusts and checks the weeping of raw, red **eczema**. For this purpose a piece of lint soaked in the lotion is applied to the raw surface and then covered with oil silk to check evaporation. Alkalies are useful in insect bites.

Internally.—While alkalies are either indifferent or disturbing to normal digestion, they are of great value in digestive troubles. In **dyspepsia**, where the gastric secretion has become thin and watery, the bicarbonates are given a few minutes before food; and when there is epigastric pain, heartburn or acid eructations, they are best administered after food. In **gastric irritability**, or to render the blood and urine alkaline, they are given in effervescing form. In gastric catarrh and chronic gastritis, such as the alcoholic form, alkalies dissolve mucus which by forming an impermeable coating prevents formation of the gastric juice. In these cases lavage of the stomach is of value to clear the stomach of its mucus and prepare it to receive food. For this purpose the bicarbonate of soda is commonly used (60 grs. to 1 pint of hot water). Given about twenty minutes before food it tends to call forth the "appetite juice" and is often combined with aromatics and bitters.* In cases of **hyperchlorhydria** and **duodenal ulcer** it will relieve the pain if given two hours or more after the meals, and when there is much fermentation and formation of organic acids it is often useful when given shortly after eating. As the gastric juice is subsequently increased it is combined with carbonate or oxide of magnesium and carbonate of calcium.† Carbonates and bicarbonates are used in an effervescing form with citric and tartaric acids, and the CO₂ formed acts as a powerful gastric sedative, and is used in vomiting, gastric irritability, etc.

Although alkalies have no direct effect in increasing the secretion of bile they are used in jaundice often with benefit.

*℞

Sod. Bicarb.	gr 15
Sp. Chlorof	ms 15
Tinct Nuc Vom	ms 10
Inf. Gent Co Rec.	ad oz 1

†℞

Sod Bicarb	oz 1/2
Mag Carb.	oz 1 1/2
Calc Carb.	oz. 1 1/2
Bism Carb	oz 1/2

Mix Half to one teaspoonful for a dose.

This it does by relieving the catarrh of the intestine which causes obstruction of the bile duct.

When a systemic action is required alkalies are best given on an empty stomach. In severe acidosis, such as may be in delayed chloroform poisoning, cyclical vomiting of pregnancy, very large doses are given by the mouth, by the continuous rectal drop method, or intravenously, of course remembering that sodium salts are preferable to the corresponding potassium salts. It is valuable in **diabetic coma**. The daily dose should be 1 to 1½ oz. freely diluted, and should be continued until the pH of the plasma is normal, and if possible until the reserve alkalinity of the plasma has been restored. Large doses have the disadvantage of producing looseness of the bowels. The use of bicarbonate should not be delayed till coma has actually set in, but should be given as soon as acidosis is recognised. It should be given freely diluted, preferably between meals. When given subcutaneously, the solution containing bicarbonate should not be boiled, as this drives off CO₂ and converts part of the bicarbonate into carbonate which is highly corrosive to the tissues and may produce sloughing. Bicarbonate of soda is added to saline solution for injection in cases of **cholera** (see sodium chloride). Alkalies have also been used in diabetes on the idea that they help oxidation of tissues, and by promoting combustion of sugar reduce the glycosuria. There is no reason to believe that they increase oxidation of tissues at all, and diabetes is not due to deficiency on the part of the tissues to oxidise sugar.

Formerly the alkalies were largely used in rheumatism on the idea that they helped excretion of uric acid. Similarly patients suffering from **gout** are treated with alkaline mineral waters. In both these conditions improvement follows but the precise nature of their action is not known and the explanation so far given is not conclusive. According to Von Noorden alkalies are not only useless in this disease but positively harmful.

As an antidote to poisoning by caustic acids, the carbonates and the bicarbonates are to be avoided as they form carbonic acid gas and so cause risk of rupture of the stomach. Caustic potash and other alkaline salts may be used in these cases.

Alkalies, especially the bicarbonates, are largely used either alone or with other **expectorants** to lessen the viscosity of the secretion in bronchitis and bronchial catarrh.*

*R

Pot bicarb	grs 15
Tinct ipecac.	ms. 10
Sp ammon aromat	ms. 20
Syr. tolu.	ms. 30
Aqua camph.	ad oz. 1

Indeed potassium bicarbonate is a common ingredient in most cough mixtures.

They render the urine alkaline in cases of excessive acidity of the urine. But as the urine tends to become acid, it is necessary to give alkalis in large doses (120 to 240 grs. of the bicarbonate) daily. Since the *coli* organisms do not grow freely in an alkaline medium, alkalis are largely used in *B. coli* infection of the urinary tract, but to be of any use large doses have to be given. These large doses of bicarbonates however often cause diarrhœa or irritation of the stomach, therefore citrates and acetates are preferred. As they hold more uric acid in solution, they are used in uric acid diathesis and uric acid calculi often with good results. It should be kept in mind that excessive alkaline urine will cause deposit of phosphates in the bladder and thus may tend to increase the formation of calculus, though not of the same variety.

Large doses of bicarbonate may cause retention of water and produce œdema. This may occur even in healthy persons and is probably analogous to salt cedema. They may also cause *alkalosis* with injury to the kidneys and retention of nitrogenous elements in the blood.

Prescribing hints.—Always prescribe the carbonate of bismuth with bicarbonate of soda and not the subnitrate, which will liberate carbonic acid gas in a mixture. The bicarbonate should be used in preference to the carbonate, and the salts of sodium in preference to potassium. Bicarbonate of soda administered with sodium salicylate tends to prevent precipitation of the irritating acid and prevents acidosis. For intravenous medication sodium bicarbonate only is used in 5 p.c. solution.

P TASSII ACETAS

Potassium Acetate (Pot. Acet.). CH_3COOK

Source.—Prepared by fusing the product of the interaction of acetic acid and potassium carbonate. Contains not less than 99 p.c. of pure potassium acetate.

Characters.—White foliaceous, satiny masses, or granular particles; deliquescent. Taste, sharp, saline; odourless, or with a faint acetous odour. **Solubility.**—2 in 1 of water, 1 in 2 of alcohol (90 p.c.).

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

NON-OFFICIAL PREPARATION

1. *Mistura Potassii Acetatis Composita*, B.P.C. *Syn.*—*Mistura Diuretica.*—Each fluid ounce contains potassium acetate, 20 grs., spirit of nitrous ether, 30 ms., tincture of hyoscyamus 20 ms., succus scoparium 60 ms., with infusion of buchu. **Dose** — $\frac{1}{2}$ to 1 oz or 15 to 30 mls.

P TASSII CIT AS

Potassium Citrate. (Pot. Cit.). $\text{K}_3\text{C}_6\text{H}_5\text{O}_7 \cdot \text{H}_2\text{O}$

Source.—Prepared by the interaction of citric acid and potassium carbonate. Contains not less than 99 p.c. of pure potassium citrate.

Characters.—White, granular crystals, or a crystalline powder. Odourless; taste, saline. *Solubility.*—1 in 1 of water.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

S I I C I T A S

Sodium Citrate. (Sod. Cit.). $C_6H_5O_7Na_3 \cdot 2H_2O$ -

Source.—Obtained by the interaction of citric acid and sodium carbonate.

Characters.—White granular crystals, or crystalline powder with a saline taste. No odour. Slightly deliquescent in moist air, efflorescent in dry air. *Soluble* in less than 2 parts of water, insoluble in alcohol (90 p.c.).

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

PHARMACOLOGY OF ACETATES AND CITRATES OF POTASSIUM AND SODIUM

Externally.—All these salts are neutral and have none of the antacid or caustic properties of liquor potassæ or alkaline salts.

Internally. **Gastro-intestinal tract.**—Acetates and citrates do not irritate the stomach and are easily borne. Being neutral they are not direct antacids like the carbonates and bicarbonates, but act as *remote antacids*. The citrates are absorbed less readily than the acetates.

Blood.—These salts are converted into bicarbonates in the body. $KC_2H_3O_2 + 4O = KHCO_3 + CO_2 + H_2O$; and thus exert an alkaline action after absorption. They have therefore the same action after absorption as alkalies, except that they do not act as direct antacids. When mixed with drawn blood the citrate inactivates calcium by forming double salts which do not liberate calcium ion, and produce typical effects of calcium deprivation. In moderate doses (10 to 50 c.c. of 10 p.c. solution in man), given intravenously, sodium citrate shortens the coagulating time of the circulating blood. The mechanism of this action is not clear and has been attributed to injury of the blood platelets, to liberation of thromboplastin, to peripheral vaso-constriction, accumulation of thrombocytes and leucocytes in the splanchnic area which accelerates hæmostasis.

Kidneys.—They are all diuretics and render the urine alkaline. Although the urine becomes alkaline yet the total amount of acids eliminated is increased. They have very slight effect on the flow in health.

Skin.—They are all diaphoretics, but the method of this action is obscure.

THERAPEUTICS OF ACETATES AND CITRATES OF POTASSIUM AND SODIUM

Internally. **Gastro-intestinal tract.**—Sodium citrate is largely used as an addition to milk (2 to 5 grs. to the ounce) to render the clots more flocculent and therefore more easy

of digestion. The citric acid prevents the ionic action of calcium and the curd consisting of sodium caseinate is much softer than calcium caseinate. Hence citrated milk is largely used in the curd indigestion of children and diarrhoea of infants. Given in large doses it causes œdema which disappears on withholding of the drug.

Blood.—These salts were formerly used in the treatment of gout and rheumatism. They act like the alkaline carbonates or bicarbonates but do not irritate the stomach or neutralise the gastric secretion. Both the acetate and the citrate are used in large doses (30 to 50 grm. per day) to raise the alkalinity of the blood in conditions of acidosis, *e.g.* in diabetic co a, without upsetting the stomach or causing diarrhoea which very often happens when bicarbonate of soda is used in large doses. Because it shortens the coagulating time, sodium citrate (9 grm. in 30 p.c. solution intramuscularly, or 6 grm. in 10 p.c. solution intravenously), has been recommended for the control of bleeding during operation or to stop hæmorrhage in gastric or duodenal ulcer.

Citrated blood is used for transfusion. The blood of the donor being kept uncoagulated by the addition of sodium citrate (1 mg. in 10 c.c. of normal saline for each 100 c.c. of blood).

Kidneys.—All these salts are used to make the urine alkaline. Thus they are used to prevent precipitation of uric acid in cases of uric acid diathesis and also to dissolve small uric acid calculi in the kidneys or bladder.

They are largely used in febrile conditions for their diaphoretic and diuretic properties* and also in general anasarca. Acetate however is less palatable than the citrate. By reducing the acidity of the urine they relieve irritability of the bladder, and are used in cystitis, and gonorrhœa in the early stage, and to prevent frequent micturition. For the same reason they are used in *B. coli* infection of the urinary tract, but large doses are required to maintain the alkalinity of the urine.

Lungs.—Because they are converted into carbonates in the blood they are used as expectorants in bronchial troubles to make the secretion less viscid.

P O T A S S I U M C H L O R A T E

Potassium Chlorate. (Pot. Chloras). KClO_3

Source.—Obtained by the electrolysis of a hot solution of potassium chloride. Contains not less than 99 p.c. of potassium chlorate.

*R

Sod Cit. gr 20

Pot Acet gr 20

Liq Ammon Acet Dil. ms 120

Syr. Aurant. ms 30

Aqua Chlorof ad oz 1

Characters.—A white powder, or colourless crystals; taste, cool and saline. With organic or oxidisable substances liable to explode if heated. **Solubility.**—1 in 16 of cold, 1 in 3 of boiling water.

Incompatibles.—Explodes when rubbed with sulphur, sulphides, charcoal, sugar, tannic acid, ammonium chloride, or glycerin. Mineral acids, ferrous salts.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATION

1 Gargarisma Chlori, B.P.C. *Syn.*—*Chlorine Gargle*—Pot. Chloras 229 grm., Acid Hydrochlor. 42 mils, Distilled Water to 1000 mils. Generate chlorine gas by mixing chlorate and acid, and dissolve gradually in water.

PHARMACOLOGY

Externally.—Coming in contact with a septic surface or discharge, the chlorate is decomposed, and oxygen is liberated. This nascent oxygen then acts as a stimulant and antiseptic to septic tissues, but it is not an antiseptic in the ordinary sense of the term, as outside the body it has very little effect even upon the most sensitive bacteria.

Internally. **Gastro-intestinal tract.**—In small doses, potassium chlorate has no action, but in concentrated solution it may through its local salt action cause severe nausea and vomiting, and after absorption considerable diuresis may arise from a similar action on the kidney.

Heart and circulation.—It has a specific action on the blood, and after a moderately large dose it disintegrates the red blood-corpuscles and converts hæmoglobin into methæmoglobin, which is set free in the serum. This effect is also observed when chlorate is added to a little drawn blood and shaken up, the mixture soon becoming reddish-brown (chocolate colour) and shows the spectrum of methæmoglobin and later of hæmatin. Since other oxidising agents produce the same effect, this action has been attributed to the oxidising property of the chlorate, but the salt is very stable and hardly possesses any oxidising power at body temperature. When this change takes place in the vessels the oxygenating power of the blood is reduced and asphyxia threatens. When however sufficient hæmoglobin remains to continue the respiration of the tissues the subacute form of poisoning results from hæmolysis. As a result of which the renal tubules become blocked with masses of hæmoglobin and fragments of the corpuscles, causing either casts to appear in the urine, or total suppression.

Kidneys.—In moderate doses (15 to 20 grs.) it acts as a diuretic, and more powerfully during pregnancy. In toxic doses, the kidneys become congested, the urine becomes bloody or dark-coloured, and at last there is complete suppression due to blockage of the tubules with degenerated corpuscles. Death occurs usually from uræmia.

Elimination.—Very little is utilised in the blood and

tissues, so that about 90 p c. of the amount given is recovered from the urine. It is also excreted from the saliva, sweat, milk, tears, and nasal mucus.

Toxic action.—It may give rise to dangerous symptoms in individuals after a single large dose, or from repeated small doses. 15 grs. caused death in a child, while an ounce has been taken without any bad effect. The toxic symptoms are nausea, vomiting, diarrhoea, scanty urine or complete anuria, urine becoming a deep reddish-brown colour due to the presence of hæmoglobin, methæmoglobin and hæmatin in solution. Icterus may appear, and the patient may die from uræmic symptoms even as late as a week after the first symptoms. All these symptoms are dependent on the action of the chlorate on the hæmoglobin of the red blood-cells. Death may result from two causes :

1. From respiratory failure and *asphyxia*, by a rapid breaking down of the red blood-cells and resulting inability of the blood to carry a sufficiency of oxygen.

2. From *uræmia*, owing to complete or partial suppression of urine following on obstruction of the renal tubules, by hæmoglobin and fragments of corpuscles.

Fatal Dose —10 grm., toxic ; 15 to 30 grm. fatal to adult.

THERAPEUTICS

Locally —The chief local use of potassium chlorate is in the treatment of different mouth and throat troubles, such as aphthous stomatitis, follicular tonsillitis, and in the tenderness and inflammation of the gums which follow the prolonged use of mercury. How it acts is not clearly understood, and the theory of its acting as an oxidising agent can hardly be explained on any rational ground. It is possible that its effects are due to salt action. A lotion (10-15 grs. to 1 oz. of water or any astringent infusion) is used as a gargle for such cases. Tablets or lozenges, of which many kinds combined with borax and cocaine are on the market, may be slowly sucked in hoarseness of the throat.

These catarrhal conditions of the mucous membrane of the mouth and fauces are greatly benefited if the local treatment is accompanied by internal administration, for the salt is excreted with the saliva after absorption, and thus locally influences the disease. Sometimes it is useful in cases of **habitual abortion**. The late author considered this drug to be a valuable diuretic in the suppression of urine in cholera.

Prescribing hints.—Potassium chlorate, being a strong oxidising agent, when prescribed with syrup of ferrous iodide, liberates iodine and forms a precipitate of hydroxide of iron. With iodide of potassium it forms a poisonous compound in the body probably iodate of potassium.

P TASSII NIT AS

Potassium Nitrate. (Pot. Nitras). KNO_3

Syn.—Purified Nitre ; Saltpetre. **Syn I.V.**—*Sora*, Beng. *Shora*, Hind.

Source.—May be obtained by the interaction of sodium nitrate and potassium chloride. Contains not less than 99 p.c. of Potassium nitrate.

Characters.—White, crystalline powder, or colourless crystals. Taste, cool, saline. *Solubility.*—1 in 4 of water. *Impurities.*—Chlorides, sulphates, lime.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

NON-OFFICIAL PREPARATIONS

1 *Charta Nitrata*, B.P.C. *Syn.*—*Saltpetre Paper*—Made by saturating white blotting paper in a 20 p.c. solution of nitre. The fumes are inhaled in *asthma*. *Ozone Papers* are similar in composition.

2 *Pulvis Lobeliæ Comp.*, B.P.C. *Syn.*—*Asthma Powder*—Potassium Nitrate 25, Lobelia and Stramonium leaves in coarse powder each 25, Tea leaves in coarse powder 25, Oil of Anise 0.1, Boiling Distilled Water 25. One teaspoonful may be burnt to fumigate a bedroom, or the fumes inhaled in *asthma*. This is a supposed imitation of *Himrod's*, *Bliss's*, and the *Green Mountain Cure*.

PHARMACOLOGY

Internally. **Gastro-intestinal tract.**—It has a cool saline taste, and in ordinary doses taken in concentrated solution may give rise to **gastro-enteritis**, with the presence of blood in the vomit and stool, muscular weakness, collapse, even coma and death. The same large doses, if taken freely diluted, cause none of these symptoms. The nitrates differ from other salts by possessing some further irritant action, and this irritant effect has been thought to be due to the reduction of the nitrate in the intestine and tissues into the poisonous nitrite. This explanation is however open to doubt. In large doses most of it is excreted as nitrate in the urine and some passes out with the saliva and sweat.

Heart and blood.—Contrary to other potash salts, it is a powerful depressant to the heart, rendering its action slower and weaker. It destroys the normal oxygenating powers of the red blood-corpuscles, and outside the body prevents the coagulability of the blood.

Skin and kidneys.—It is slightly diaphoretic, but has a powerful diuretic action. Diuresis is due partly to salt action which increases the exchange of fluids between the blood and lymph, thus promoting the filtration in the kidney. Practically the entire quantity is excreted unchanged, a small portion may be reduced to nitrites.

THERAPEUTICS

Internally.—It was formerly employed in almost every febrile and inflammatory disease, but now only on rare occasions. It is a useful remedy for arresting the onset of a **gouty attack**, or for removing the headache due to a debauch. 20 grs. of nitrate with 30 grs. of potassium bicarbonate in a tumbler of soda water is the best method of administration in such cases. As a diuretic it is chiefly used in conjunction with other diuretics, but the acetates and citrates are always preferred. As an inhalation it cuts short an asthmatic fit, and hence it is the basis of many nostrums, such as *Himrod's Cure*, *Green Mountain*, etc. *Charta nitrata* or *charta nitrata et chlorata* can be burnt, and the fumes inhaled.

Caution.—Its use is to be avoided in inflammation of the stomach, intestines, bladder and kidneys, and cardiac weakness.

S O D I U M

Sodium Chloride. (Sod. Chlorid.). NaCl

Syn.—Common Salt.

Source.—May be obtained by purifying common salt.

Characters.—Small, white, crystalline powder, or transparent, cubical crystals, free from moisture Taste, saline Odourless. *Solubility.*—1 in 3 of cold water, 1 in 10 of glycerin.

OFFICIAL PREPARATIONS

1. *Injectio Sodii Chloridi et Acaciæ.*—Sodium chloride 0.9 p.c. and acacia 6 p.c.

2. *Liquor Sodii Chloridi Physiologicus.* *Syn.*—*Normal Saline Solution*; *Physiological Saline Solution.*—Sodium chloride 0.9 p.c. Should be prepared with sterilised water for intravenous injection, and should be used within one month after its preparation, and if kept in sealed containers for a longer period.

NON-OFFICIAL PREPARATIONS

1 *Liquor Dextrosi et Sodii Chloridi, B.P.C.* *Syn.*—*Glucose-saline Solution.*—Dextrose, 50, sodium chloride, 9; sterile water to 1000.

2 *Liquor Ringer, B.P.C.* *Syn.*—*Ringer's Solution*—Sodium Chloride 70, potassium chloride, 0.14; calcium chloride, 0.12, sodium bicarbonate, 0.2, distilled water to 1000.

3 *Liquor Ringer-Locke, B.P.C.* *Syn.*—*Ringer-Locke Solution*—Sodium chloride, 90, potassium chloride, 0.42, calcium chloride, 0.24, Dextrose, 10, sodium bicarbonate, 0.5, distilled water to 1000

SALT ACTION AND PHARMACOLOGY OF SODIUM CHLORIDE

The salt action only affects living tissues by changing the physical properties of the fluids contained in them or surrounding them. In the body the epithelial cells of mucous membranes, the endothelial cells of vessels, and the cells of the renal glomeruli act as semipermeable membrane, *i.e.* a membrane through which the solvent can pass, but none or very little of the dissolved substance. If two equimolecular solutions are separated by such a semipermeable membrane, the osmotic pressure is equal on the two sides, and the solutions are then said to be isotonic, and no exchange of constituents occur between the two fluids. Pharmacologically the term *isotonic* means a solution having the same osmotic tension as that of the blood. If however a given volume of one of these fluids has a higher molecular concentration than the other, it is said to be *hypertonic* (or hyper-isotonic), and an interchange between the two fluids takes place, water being attracted from the hypotonic to the hypertonic solution, and to a smaller extent the substances held in solution pass from the hyper to the hypotonic solution, thus shortly rendering the two fluids once more isotonic.

In the human body with its already noted semipermeable

membrane the process of osmosis is continually going on whenever fluids of varying tonicity meet. As an example, red blood cells shrink in size when they are placed in a solution of salt stronger than blood plasma (hypertonic), because the water is withdrawn from them. In hypotonic solution they swell up as they absorb water and eventually burst liberating hæmoglobin to the surrounding tissues, while in isotonic solution they remain unaltered in size.

The muscles are similarly affected, hypertonic solutions withdraw fluid, while weaker ones are absorbed into the muscle. As the muscles are rendered dry and hard, and thus unsuitable for microbic growth, salting is used in the preservation of meat and fish. Strong salt solutions by withdrawing their fluid contents irritate the exposed nerves

As these osmotic exchanges are continually going on in the human body, its importance in the preservation of the balance of the constitution of the body fluids can hardly be exaggerated, and as has been pointed out it is purely a physical process which goes on passively without the expenditure of vital activity which entails a drain of energy of the organism. Thus the process of osmosis may be regarded as a great conservator of energy, of respiratory interchange, and metabolism.

Sodium chloride is an essential constituent of the body and perhaps the chief mineral constituent of the blood serum. It is therefore essential that the necessary supply of this substance should be introduced either with the food itself, or as an addition to the food. As it is always present in the body in large quantities and exerts no specific action, it presents a perfect example of salt action which action varies in proportion to the concentration of salt in solution.

Alimentary tract.—Salt has a characteristic taste and strong solutions are astringents. It has very little effect on digestion, and the absorption of food is very little altered when salt is added to food. It is possible, however, that a small quantity of salt in the food may render it more palatable and thus induce a reflex flow of gastric juice. Strong concentrated solutions withdraw fluid from the mucous membrane of the stomach causing shrinkage of the cells and thus cause irritation and act as emetics. Very little is absorbed from the stomach. There is a constant tendency of fluid and some salts to pass inwards from the lumen of the bowels, and being of lower osmotic pressure than the blood serum, hypotonic solution is absorbed from the bowel readily. Isotonic solution is more slowly absorbed; while hypertonic solution is absorbed with difficulty, not till it has withdrawn fluid and increased in volume to make it isotonic. This accumulation of fluid may cause purgation, but since it is easily absorbed purgation rarely follows.

Blood.—The changes on the blood after an intravenous injection depend upon the nature of the solution used, whether *isotonic*, *hypertonic*, or *hypotonic*. When a hypertonic solution is used, the blood becomes concentrated, and draws more lymph into the blood by osmotic attraction to regain its normal composition, this increased volume of the blood in its turn tends to augment the flow of lymph, urine and sweat; and since the normal balance of plasma and corpuscles must be restored, it sets up currents between the blood and the fluid of the surrounding lymph. All these changes are accompanied by a large rise of capillary pressure in the abdominal viscera, and it is possible that the inward flow of lymph is the outcome of this pressure.

As a result of these changes in the blood and lymph there is an increased activity of the excretory organs. Thus there is a copious diuresis following an injection of salt solution. It has been suggested that diuresis is the result of increased volume of blood and lymph causing an inward capillary pressure in the glomerulus which promotes the escape of fluid into the capsule. But the more plausible explanation is that the presence of salt and water in excess in blood, following an injection, leads to an increased interchange of water between the tissues and blood making the latter diluted, thus increasing the non-colloidal constituents of the blood and allowing better filtration and more fluid to pass through the glomeruli into the tubules.

Cerebrospinal pressure.—Injection of hypotonic solution or distilled water into a vein causes transient increase of venous pressure and a marked and prolonged rise of cerebrospinal fluid pressure. If hypertonic (30 p.c. NaCl) solution is injected intravenously the cerebrospinal fluid pressure after a short rise falls profoundly and remains low for a period of several hours. This effect is independent of the arterial pressure and is probably due to (a) rise of the osmotic pressure of the blood causing fluid from the brain substance and cerebral spaces to pass into the blood vessels, or (b) reverses the normal direction of the cerebrospinal fluid flow.

Excretion.—Salt is excreted chiefly by the urine as potassium chloride, a small portion being lost by the faeces and sweat. Its excretion is diminished in some cases of nephritis, in pneumonia and during growth of new tissues (cancer). Its excretion is hastened by the administration of bromides, iodides, nitrates and thiocyanates, while its use hastens the excretion of these salts, and may be useful in bromism and iodism.

THERAPEUTICS

Cold douching with salt and water is a very valuable

remedy in all forms of muscular weakness, specially in the weak back of growing girls.

Salt being mild irritant, sea bathing acts as a general stimulant to the skin by improving the circulation and nutrition and produces a reflex tonic effect. This is the common experience after sea bath. If the patient is unable to proceed to the sea side, Tidman's sea salt, or ordinary rock salt (one pound to three gallons of water), is an efficient substitute. It is doubtful if salt baths exert any influence on metabolism although it is often recommended in diverse conditions. At Droitwich and Nantwich concentrated hot salt baths (20 p.c.) are used for **chronic rheumatism, sciatica, and joint diseases**, where the patients not only have daily baths but drink sufficient water on the idea that the tissues will be more thoroughly washed out and waste products will be removed from the system. It is doubtful if this helps more excretion of uric acid from the system, but the fact remains that patients do show improvement under such treatment. The reasons for improvement are perhaps change of climate, a well regulated life and the faith in the healing power of salt water. **Dyspepsia, wasting, and chronic skin affections of adults, and gastritis and entero-colitis in infants** have been treated with injections of sea water.

Wright's solution (sodium chloride 4, sodium citrate 1, water 120), or hypertonic saline are used in the physiological treatment of septic wounds, and as lotions for washing ulcer and sinuses, specially in diabetics where strong antiseptics damage the tissue. The usual practice is to pack the wound with gauze soaked in the solution, or to irrigate the wound with the lotion. Efficiency of this treatment is due to the hypertonic saline acting as a lymphagogue, which liberating a tryptic ferment from the leucocytes cleanses the wound and checks microbial growth.

Eighty grains (0.9 p.c.) of common salt in one pint of water constitutes normal saline solution, which is isotonic with the blood, which may be injected either into the veins, the rectum, or the loose connective tissue under the axilla or breast, in (1) **shock or collapse** from any cause, such as severe hæmorrhage or dehydration, to restore the fluid needed for the heart to work efficiently; (2) **certain toxæmic conditions, e.g. uræmia or eclampsia**; (3) **carbon monoxide poisoning**; (4) **profound malnutrition and prostration**; and (5) **hypertonic solution intravenously in cerebral œdema and intracranial pressure**. In the treatment of shock its value is not very favourable and the blood pressure is not maintained for long; moreover large injections may cause fatal dilatation of the heart. In temporary collapse its value is better. For the relief of urgent symptoms in cerebral tumour, uræmia and meningitis, it has been given intravenously (30 c.c. of 20 to 30 p.c. solution). It has been used with less justification in

cases of head injury, postconcussional syndromes, and in severe headaches of various types.* Improvement resulted when there was definite rise of intracranial pressure. It has however been shown that the fall of pressure is followed by a rise with secondary œdema of the brain due to the fixing of the salt by the brain cells.† In conditions of toxæmia it does not help elimination of poison by itself, though it may cause considerable dilution of the poison. It is commonly given intravenously, the usual quantity introduced being 500 to 1500 c c. (1 to 3 pts.). The most commonly employed solution is normal saline containing a full teaspoonful of salt to 1 pint of *ordinary water*, as this usually contains some calcium. If made up with distilled water and given intravenously, pure sodium chloride may have a poisonous effect. The addition of 0·5 p.c. of sodium bicarbonate to the physiological saline solution approaches more closely the normal reaction of the blood, counteracts acidosis and ensures more lasting restoration of the blood-pressure.

The effects of these saline infusions vary according to whether the volume of the blood has been previously decreased or not. If there has been no previous diminution in the volume of the blood, a saline infusion has no effect in raising arterial pressure and may lead to anasarca. On the other hand if the volume of blood has been diminished by hæmorrhage, a saline infusion will not only increase the volume of the blood and so maintain arterial pressure, but by shortening the coagulation time will favour cessation of hæmorrhage.

Since colloids leave the vessels slowly and help to retain the transfused fluid, they diminish diuresis, lymph filtration and œdemas. Acacia and gelatin therefore were added to saline solution to maintain the blood pressure for a longer time in cases of shock and hæmorrhage than when treated with plain non-colloidal saline infusion. But the results have not been very encouraging, although they appeared to be of some value at first. Severe and even fatal reactions after the use of acacia, some from faulty technique and others from special susceptibility to the drug, have been recorded. It alters the colloidal equilibrium of the blood which tends to agglutination of the corpuscles and to other anaphylactoid phenomena (Hanzlik).

It is very largely used, and with very good results, in the treatment of cholera, in which as much as three pints of hypertonic solutions are used. The usual formula for hypertonic solution consists of sodium chloride 120 grs., pot. chloride 6 grs., calcium chloride 4 grs. to 1 pt. of water. To this is added sodium bicarbonate 40 grs. and glucose 14 grs.

*H Hoff, *Medical Annual*, 1934.

†Weed and McKibben, *Amer. Jour. Physiol.*, 1919.

The bicarbonate of soda maintains the alkaline buffer-value of the blood and counteracts tendency to acidosis. In cases of severe shock or collapse a small infusion containing adrenaline helps to promote the maintenance of blood pressure. It is also used intravenously, subcutaneously, or per rectum in other forms of dehydration, as for instance in acute bacillary dysentery. Besides overcoming collapse, the chloride combines with the toxins and helps them to be excreted *via* the kidneys. Salines should not be given in any form of œdema, especially that of the lungs.

Internally.—Cold salt and water is an excellent gargle for chronic relaxed throat, and also a very effective nasal douche. It is a prompt and efficient emetic, and it may be injected into the rectum for the cure of thread-worms. It is an antidote in poisoning by silver nitrate, which it converts into the insoluble chloride. It is also useful in cases where a leech has been swallowed or has got up the nose.

Saline solution is introduced into the rectum, not more than 4 oz. at a time, either alone or with dextrose (1 oz. to 1 pt.) to maintain the strength of the patient, to combat dehydration, and as a diuretic.

Untoward effects.—Excessive injection of salines may produce glycosuria, slight fever and rarely albuminuria. It may cause death by pulmonary œdema, and over distension of the heart.

Note.—Since retention of salt in the tissues may lead to œdema, a salt free diet has been recommended to reduce œdema with salt retention. Salt free diet sometimes lowers blood pressure and has been advised in primary hypertension.

S I T I SULP AS

(Sod Thiosulph)

Sodium Thiosulphate. $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$

Source.—May be prepared by the action of sulphur on sodium sulphite.

Characters.—Colourless, transparent, monoclinic, prismatic crystals; odourless; taste, saline. Efflorescent in warm dry air; slightly deliquescent in moist air. Soluble in 0.5 part of water at 25°C .; insoluble in alcohol (95 p.c.).

B.P. Dose.—5 to 15 grs or 0.3 to 1 grm. by *subcutaneous, intramuscular or intravenous injection.*

ACTION AND USES

It is largely used as a reducing agent in photography under the name of "Hypo," and has been used in the form of a lotion (1 in 10) as a parasiticide in various skin affections, *e.g.* eczema, furunculosis, etc, and internally as a purgative, in doses of 1 grm. in water, repeated every 2 hours if necessary. Nowadays it is used intravenously in exfoliative dermatitis, specially those appearing after the use of organic arsenic preparations. It is also used against

other manifestations of arsenic poisoning. It has been suggested that it converts the arsenic into less harmful compound but definite proof of this is not forthcoming. The usual method is to give it intravenously in doses of 0.3, 0.45, and 0.6 grm in 5 c.c. of distilled water every second or third day. It may be administered in 15 gr. doses by the mouth dissolved in normal saline. It has been recommended in mercurial and bismuth stomatitis and is useful in all acute poisoning from metals. It acts by dissolving the storage depots and helping elimination by the kidneys, but when a large dose is used a large quantity is suddenly dissolved out which the kidneys cannot eliminate so that it actually increases the poisoning. It has been used intravenously in cyanide poisoning, when it forms sulphocyanate which is practically non-toxic.

LIQU S II ET YLATIS

(Not Official)

A syrupy liquid, colourless when fresh, turning brown on keeping

It is used as a depilatory, and to destroy warts, moles, and nævi. Apply lightly with a pointed glass rod for 2 or 3 successive days till a scab forms. When this falls off, repeat the treatment if necessary. If pain results, allow a drop of chloroform to fall upon the spot.

S II SULP OCYANAS

(Not Official)

Syn.—Sodium Thiocyanate Sodium Rhodanate.

Dose —1 to 5 grs. or 0.06 to 0.3 grm

Uses.—Supposed to be one of the most efficacious remedies in the treatment of hypertension in doses of 5 grs three times daily after meals. Sometimes nausea, gastro-intestinal disturbances and nervous irritability may follow its use. Others suffer from diarrhoea, muscular fatigue, motor aphasia, hallucination of sight and hearing, delirium, convulsive twitchings, coma and death. In some cases the symptoms resemble those of iodism. It has not proved a success. The potassium salt causes more distressing nausea and weakness. If the patient does not show any satisfactory improvement after 5 gr. doses, taken for two months, the drug will have no effect.

AM ONIU

Ammonia (Not official)

Ammonia preparations may be grouped into two classes, (a) those that liberate irritating ammonia from their compounds, and whose action therefore depends upon free ammonia; (b) those forming salts homologous with alkali metals, and which act as salts in the body.

1. Preparations whose actions depend upon free ammonia

LI U R A NIAE F TIS

(Liq Ammon Fort)

Strong Solution of Ammonia

Source.—Obtained by heating a mixture of ammonium chloride and slaked lime, and passing the gas (ammonium) into distilled water. Contains 32.5 p.c. of w/w ammonia.

Characters.—A clear, colourless, alkaline liquid; odour, characteristic; very pungent. Sp. gr. 0·885 to 0·891.

Incompatibles.—Acids and acid salts, metallic salts and alkaloids.

OFFICIAL PREPARATIONS

1. *Liquor Ammoniaë Dilutus.* *Syn.*—*Liquor Ammonice; Ammonia Solution.*—10 p.c. w/w of ammonia. B.P. Dose.—10 to 20 ms. or 0·6 to 1·2 mils.

2. *Linimentum Camphoræ Ammoniatum* —25 p.c. Liq. ammon. fort.

3. *Spiritus Ammoniaë Aromaticus.*—*See* Ammonium Carbonate, page 90.

PHARMACOLOGY

Locally.—A solution of ammonia when rubbed in or applied to the skin stimulates the peripheral nerves and superficial blood-vessels, producing a sensation of heat and redness. Being more volatile than the fixed alkalies it penetrates more rapidly and deeply and is corrosive in its effects. If it is concentrated and evaporation prevented it does not dissolve the epidermis but penetrates through it and produces blister. Ammonia is therefore a rubefacient and vesicant.

Nose and air-passages.—The vapour of ammonia powerfully irritates the mucous membrane of the nose and air-passages causing sneezing. It also irritates the conjunctiva producing lachrymation. By exciting the nasal afferent nerves, it reflexly stimulates circulation and respiration, and accelerates pulse rate. If the inhalation is prolonged, or the vapour is too concentrated, inflammation of the nasal and air-passages results.

Internally.—On reaching the stomach, ammonia at once reflexly stimulates the heart and circulation by its action on the accelerator centre. Like other alkalies it neutralises the acidity of the gastric juice if given during digestion, with the formation of ammonium chloride. It also increases peristalsis and causes a sense of warmth in the stomach. Therefore, it is an antacid, gastric stimulant and carminative. In large doses it is a gastro-intestinal irritant.

Absorption.—Although ammonia is readily absorbed from the alimentary canal it does not produce any special physiological effect when administered through this channel. If not converted into a chloride by the acid in the stomach it appears in the portal blood as carbonate or carbamate, and carried to the liver where it is converted into urea. The liver is therefore an important factor in the disposal of ammonia, and if the organ is functioning properly, it can prevent the passage of ammonia to the systemic circulation. The systemic effects are only observed after subcutaneous or intravenous administration. The characteristic action of ammonia base is first stimulation followed by paralysis of the central nervous system, specially the medulla. On the cord its effect resembles strychnine and causes reflex irritability

followed by convulsion; while it paralyses the motor nerve-endings like curara.

Blood.—Since ammonia is converted into urea in the blood its action differs from the fixed alkalies in not increasing the available alkalinity of the blood.

Heart and circulation.—The immediate result of the reflex effect is vaso-constriction and stimulation of the accelerator centres followed by a rise of blood pressure and stimulation of the heart. But owing to the rapid change of the drug in the system this is of momentary duration.

Lungs—After inhalation or when swallowed, ammonia reflexly stimulates the respiratory centre from local irritation. Respiration is also increased by direct stimulation of the respiratory centre after absorption.

Nervous system.—Ammonia is a general stimulant, and by its action on the medulla, it stimulates respiration, constricts the peripheral arterioles, and raises the blood-pressure. These effects are reflex from surface irritation, for they are almost instantaneous and manifest themselves before the drug can be absorbed. In toxic doses, it produces convulsions, due to the stimulation of the motor cells in the cord.

Kidneys.—Ammonia and its salts are changed into urea in the liver. They differ from the fixed alkalies in not increasing the alkalinity of the blood and having no effect on the urine except to increase the urea and thus causing some diuresis.

Elimination.—Ammonia is thrown off with the breath, sweat, urine and bronchial secretion.

Toxic action.—If a large dose of a concentrated solution be swallowed, it may cause death within a few minutes from suffocation due to spasm of the glottis. Otherwise the symptoms are those of poisoning by a corrosive alkali.

Antidotes.—The same as those of the other alkalies.

THERAPEUTICS

Externally—As a *local stimulant* to nerve and blood-vessels, the liniment of ammonia is rubbed over stiff joints, and in various conditions of chronic rheumatism; and as a *counter-irritant* on the chest in bronchitis, pneumonia and pleurisy. Ammonia may be used as a *vesicant* in cases where cantharidin is contra-indicated. A piece of lint cut slightly larger than the intended blister is moistened with the strong solution and applied and immediately covered over with a watch-glass. Ammonia neutralises the poison of nettles and insect-bites and thereby lessens the pain and swelling caused by them.

The vapour (smelling-salts) is used to rouse patients from fainting, shock, syncope, stupor and narcotic poisoning.

Internally.—Like other alkalies, ammonia may be given in acid dyspepsia. Spirit of sal volatile is a useful remedy for gastric and intestinal cramps; a few drops with bicarbonate

of soda and dill water give relief to flatulence in infants. As a general diffusible stimulant, ammonia is extremely serviceable in syncope, shock, fainting, and in the low adynamic conditions of febrile diseases, *e.g.* pneumonia, typhoid, etc. It makes an excellent "pick-me-up,"* and softens the phlegm in bronchitis and catarrhal pneumonia, but the carbonate is better. Ammonia controls *iodism*, and is therefore combined with iodides when prescribed in large doses.

A M NII CA NAS

(Ammon. Carb.)

Ammonium Carbonate

Syn.—Ammonium Sesquicarbonate.

Source.—A variable mixture of ammonium bicarbonate, NH_4HCO_3 , and ammonium carbamate, $\text{NH}_4\text{NH}_2\text{CO}_2$, obtained by subliming ammonium sulphate and calcium carbonate.

Characters.—In translucent, crystalline masses; odour ammoniacal; reaction alkaline. Taste, pungent, ammoniacal. Effloresces when exposed to air, it partially dissociates and volatilises, and is converted into porous lumps or a white powder. *Solubility.*—1 in 4 of water.

Incompatibles.—Acids, acid salts, lime water, metallic salts, alkaline earths and alkaloids.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATIONS

1. *Liquor Ammonii Acetatis Fortis*, *see* page 93
2. *Spiritus Ammoniae Aromaticus*. *Syn.*—*Spirit of Sal Volatile*.—Contains 2.1 to 2.4 p.c. w/v of ammonia. **B.P. Dose.**—15 to 60 ms. or 1 to 4 mils.

A M NII ICA NAS

(Ammon. Bicarb.)

Ammonium Bicarbonate

Source.—May be prepared by passing carbon dioxide into solution of ammonia. Contains not less than 98 p.c. and not more than the equivalent of 102 p.c. of ammonium bicarbonate.

Characters.—White crystals, or fine, white crystalline powder. Taste, pungent, odour ammoniacal. Slightly hygroscopic. Volatilises slowly at ordinary temperature. *Soluble* in $5\frac{1}{2}$ parts of water; insoluble in alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The carbonate and the bicarbonate possess all the virtues of the liquor, and in addition are powerful expectorants, facilitating the expulsion of viscid mucus. The carbonate is largely used in cough mixtures as it renders the mucus of respiratory tract more fluid. As it is not excreted by the bronchial mucus or by the lungs, its expectorant action is due to the fact that unchanged

*R:

Sp. Ammon Aromat	ms. 30
Sp. Ether	ms 15
Sp. Chlorof	ms 15
Tinct Cardam Co.	ms 30
Aqua Camph	ad oz. 1

carbonate of ammonia acts as a nauseant to the stomach and thereby increases the bronchial secretion by reflexly exciting the vagus supplying the mucus glands. They are therefore very useful in bronchitis, and catarrhal pneumonia.* Given in large doses, or even in small repeated doses, over a long period. they are irritants to the bowels and may give rise to diarrhœa. They should therefore be given with caution in cases complicated with diarrhœa. The carbonate is an emetic in 30 gr. doses, though rarely used for the purpose. In the form of aromatic spirit of ammonia it is used as a mild stomachic in debility and alcoholism, and as a carminative in flatulence.

The carbonate of ammonia and the spiritus ammoniæ aromaticus are incompatible with acids and should not be prescribed with any syrup with an acid reaction, e.g. syrup of squill. Although carbonates precipitate free alkaloid from watery solution of most alkaloidal salts, codeine and atropine are not precipitated by it. Syrup of tolu and liquid extract of liquorice cover its taste well.

2. Preparations which act as salts in the body

A N H C L I U

(Ammon Chlorid)

Ammonium Chloride. NH_4Cl

Syn.—Sal Ammoniac. Syn. I.V.—*Nishadal*, Beng. *Noshadar*, Hind.

Source.—Prepared by neutralising ammonia with hydrochloric acid.

Characters.—White, crystalline, granular powder; odourless. Taste, saline, cooling. *Solubility*.—1 in 3 of water, 1 in 60 of alcohol (90 p.c.).

Incompatibles.—Alkalies and their carbonates, mineral acids; lead and silver salts.

B.P. Dose.—5 to 60 grs. or 0.3 to 4 grms.

NON-OFFICIAL PREPARATIONS

1. *Lotio Ammonii Chloridi*. Syn—*Lotio Evaporans*, B.P.C.—Ammonium chloride gr 300, alcohol (90 p.c.) oz. 2½, water to oz 20

2 *Vapour Ammonii Chloridi*.—Obtained by mixing hydrochloric acid and ammonia in a suitable apparatus and purifying through water or moist sponge. A useful inhalation in *bronchitis*, and in affections of the throat and eustachian tube.

PHARMACOLOGY AND THERAPEUTICS

Since ammonium is converted into urea the systemic action of ammonia base is elicited when the chloride is injected intravenously or subcutaneously. It first stimulates and then paralyzes the central nervous system and the medulla; increases the reflex excitability of the cord, and causes convulsions like strychnine. The motor nerve-endings

*R

Liq ammon acet. dil	ms 120
Ammon carb	gr 4
Pot bicaib	gr. 15
Tinct ipecac	ms 10
Syr tolu	ms 30
Inf seneg rec	ad. oz. 1

are paralysed in frogs, though no such effect is observed in mammals. During convulsion the respiration is arrested and the blood pressure rises enormously. Death takes place from asphyxia, but if the animal is kept alive by artificial respiration recovery takes place owing to elimination of the salt.

The rise of blood pressure is due to constriction of the peripheral vessels through the vaso-motor centre, and the heart becomes slow from stimulation of the vagal centre from increased blood pressure.

Externally.—Locally applied, a solution of the chloride has a soothing refrigerant effect, and this effect is greatly increased by the addition of alcohol or potassium nitrate. A lotion is therefore used in cases of injury to different parts, such as sprains, bruises, etc., as a cooling application, and Lotio Evaporans is used for the purpose. The vapour, when inhaled, increases the secretion of the mucus from the larynx, pharynx, trachea, bronchi, eustachian tube, etc., and is therefore serviceable in chronic pharyngitis, laryngitis, bronchitis, and otitis media.

Internally.—It is an irritant and astringent and causes a reflex flow of saliva. From the stomach it is rapidly absorbed and is not converted into urea to the same extent as when the carbonate is used. In herbivora it forms urea and liberates chloride ions to combine with sodium and potassium, forming chlorides and are eliminated as such, thus *reducing the fixed alkalies* of the body giving rise to acidosis. This action takes place in man to a less extent. Because it causes acidosis and helps the plasma to hold more calcium in solution it is used in tetany and to counteract alkalosis.

In the form of lozenges, when allowed to melt slowly, in the mouth, it acts as a reflex expectorant. In moderate doses (10 to 15 grs.), it is a gastro-intestinal irritant, particularly to the intestine.

Liver.—It is used as an indirect cholagogue in catarrhal jaundice, and at one time was used in the treatment of threatening abscess of the liver. It is doubtful if it possesses any of these effects.

Lungs.—It makes the secretion of bronchial mucus more fluid and less tenacious and helps expectoration. This effect is partly reflex from irritation of the stomach and partly due to salt action in the bronchioles. It is therefore used as an expectorant in bronchitis, both acute and chronic. It is not indicated when the sputum has become more abundant and easy to expectorate. Since its effects do not last long it requires to be repeated frequently.

Kidneys.—It is a diuretic, due partly to urea and partly to the reduction in the amount of salts adsorbed by the tissue proteins, and the salts so liberated increase the non-colloidal constituents of the blood thus reducing the resis-

tance to filtration and act as diuretics. It is used with mercurial diuretics to increase their diuretic effect. The usual method is to administer the salt by the mouth in 15 to 20 gr. doses followed by injection of mersalyl. It renders urine acid.

Excretion—It is partly excreted as such, but a large portion as urea.

L I U A N I I A C E T A T I S F T I S

(Liq. Ammon Acet Fort)

Strong Solution of Ammonium Acetate

Source.—Obtained by the action of glacial acetic acid 453 G., ammonium carbonate 330 G., strong solution of ammonia 100 mls or q.s., water sufficient to produce 1000 mls.

Characters.—A thin, syrupy liquid with an odour of ammonia and of acetic acid. Sp. gr. 1.098.

B.P. Dose.—15 to 60 ms. or 1 to 4 mls.

OFFICIAL PREPARATION

1. **Liquor Ammonii Acetatis Dilutus.** *Syn.*—*Liquor Ammonii Acetatis*; *Minderer's Solution.*—12.5 p c. of strong solution of acetate.

B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 8 to 30 mls.

NON-OFFICIAL PREPARATION

1. **Liquor Ammonii Citratis Dilutus**—Ammonium carbonate 87.5 G., citric acid 125 G., water to 1000 mls *Dose.*—2 to 6 dis or 8 to 24 mls

PHARMACOLOGY AND THERAPEUTICS

The solutions of the acetate and citrate are diaphoretics and diuretics*. The diaphoresis is due to their effect on the sweat centre. If the patient is kept cool, their action concentrates upon the kidneys and there is diuresis. The diuresis is due to the formation of urea in which form they are eliminated. For these actions, they are used as mild, non-depressant antipyretics in fevers.

L I T I I C A N A S, . P. C.

Lithium Carbonate. (Not official)

Source—Obtained from native silicates of lithium

Characters—In white powder, or minute crystalline grains Taste, slightly alkaline *Solubility.*—1 in 80 of water, insoluble in alcohol (90 p c).

Dose—2 to 5 grs. or 0.12 to 0.3 grm

L I T I I C I T A S, . P. C.

Lithium Citrate. (Not official)

Source.—Prepared by the interaction of citric acid and lithium carbonate.

Characters.—A white crystalline, deliquescent salt. Taste, saline, cooling. *Solubility*—1 in 2 of water

Dose.—5 to 10 grs or 0.3 to 0.6 grm

*R₂

Liq ammon acet dil	ms 120
Pot acetat vel citrat	grs 20
Sp. ether nitros	ms. 15
Syr aurant	ms 60
Aqua chlorof.	ad oz. 1

PHARMACOLOGY

Lithium salts are readily absorbed and resemble the corresponding potassium salts in their actions, and render the urine alkaline acting like other fixed alkalies. They are powerful gastro-intestinal irritants when used in a concentrated form or in large doses or even when given subcutaneously. They are diuretics, acting chiefly by salt action, and it was claimed that their prolonged use would dissolve uric acid calculi. But lithium acts as a solvent for uric acid only when present in relatively large amounts, since the quadriurate is not rendered soluble by any lithium salt except in concentrations which would be toxic to man. Moreover, there is no evidence, clinical or otherwise, to show that lithium is more valuable than potassium. These salts are rarely used now.

CALCIUM CARBONATE

(Calc. Carb.)

Calcium Carbonate. CaCO_3

Syn.—Precipitated Calcium Carbonate. Syn. I. V.—*Khari*, Beng.

Source.—Obtained by the interaction of a soluble calcium salt and a soluble carbonate. Contains not less than 98.5 p.c. Calcium Carbonate.

Characters.—A white, micro-crystalline powder, insoluble in water. Odourless and tasteless.

Incompatibles.—Acids and acid salts.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

CHALKChalk. (Cret.). CaCO_3

Syn.—Creta Præparata.

Source.—Native calcium carbonate purified by elutriation.

Characters.—White, or greyish-white, friable masses, or powder. No odour or taste.

Incompatibles.—Acids and sulphates.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

Enters into —Hyd. c. Creta. and the

OFFICIAL PREPARATIONS

1. Pulvis Cretæ Aromaticus.—25 p.c. chalk. B.P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

2. Pulvis Cretæ Aromaticus cum Opio.—2.5 p.c. opium or $\frac{1}{4}$ gr. morphine in 60 grs. B.P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

NON-OFFICIAL PREPARATIONS

1. Mistura Cretæ Co., B.P.C.—Pulv. Cretæ Arom. 180 grs, Chalk 180 grs, Sp Ammon Aromat. 180 ms, Tinct Catechu $1\frac{1}{4}$ oz., Tinct Card. Co 360 ms, Tinct. Opi 60 ms., Sucrose 1 oz, Tiagacanth Powder 40 grs., Cinnamon Water to 20 oz. Dose.—1 oz or 30 mls.

2. Mistura Cretæ, B. P. C. Syn—Chalk Mixture.—Prepared chalk 30 G, tragacanth powder 5 G, sucrose 60 G, cinnamon water q s to 1000 mls Dose.— $\frac{1}{2}$ to 1 oz or 15 to 30 mls

PHARMACOLOGY

Locally chalk is a mild astringent and desiccant.

Internally. Ali entary canal.—Chalk acts as a direct local antacid, neutralising free acids in the mouth and stomach. If not already acted upon it passes readily into the intestine, where it acts as an antacid and a non-irritating

astringent, caused by (1) the neutralisation of any acid it meets, with formation of chloride or lactate and thus reducing the secretion; (2) formation of a protective coating over the intestinal mucous membrane which also diminishes reflex peristalsis; (3) adsorption of toxins; and (4) depressant action on the intestinal canal due to calcium ion. Lime salts are feebly absorbed on account of their low diffusive power and are excreted with the fæces.

Kidneys.—Some think that calcium carbonate is a diuretic because certain mineral waters, such as Contrexeville and Vittel containing calcium bicarbonate and sulphate, among other salts, have been found useful solvents for uric acid. But there is no direct evidence.

THERAPEUTICS

Externally—Chalk may be used as a dusting powder in excoriations, burns and weeping eczema. Duckworth uses it in the form of an ointment (1 in 1 of benzoinated lard) in erysipelas.

Internally. **Alimentary tract.**—Chalk is used as a basis for almost all the tooth powders. As an *antacid* it may be used in acid dyspepsia, but lime water acts much better. Aromatic chalk powder is an excellent remedy for mild diarrhœa, especially that of children with sour-smelling stools. If the diarrhœa is caused by some irritating food, a dose of castor oil should precede its use. In diarrhœa chalk acts like bismuth salts by forming an insoluble coating over the mucous membrane, and may be combined with it in diarrhœa.* It is also used as an antacid in hyperacidity and in gastric and duodenal ulcer often in combination with carbonate or oxide of magnesium (*see* page 73). Lime salts are of special value in acid poisoning, especially in oxalic acid poisoning, as they form insoluble oxalates.

Prescribing hints.—Generally given in the form of chalk mixture with opium and astringent tinctures. Aromatic chalk powder with bismuth and grey powder is very useful in *infantile diarrhœa*.†

CALCIUM CHLORIDE

(Calc. Chlorid.)

Calcium Chloride. CaCl_2

Source.—Formed by neutralising hydrochloric acid with calcium carbonate, evaporating the solution, and desiccating at a temperature not exceeding 200°C . Contains not less than 98 p.c. Calcium Chloride.

Characters.—In dry, white granules or porous deliquescent masses.

*R

Bism. carb gr 10
Pulv. cret. aromat gr 10
Pulv. ipecac. et opii gr. 5

For one powder.

†R

Hydrarg. c. cret. gr $\frac{1}{8}$
Bism. carb. gr. 2
Pulv. cret. aromat. gr. 4

N.B.—Dover's powder may be omitted if necessary.

Taste, warm, slightly bitter. *Solubility*.—1 in 1·5 of water, 1 in 3 of alcohol (90 p.c.).

Incompatibles.—Carbonates, phosphates, sulphates, and tartrates.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grms.

N.B.—When calcium chloride is prescribed for injection, twice the prescribed amount of hydrated calcium chloride shall be dispensed.

CALCIUM HYDRATUM

(Calc. Chlorid Hydrat)

Hydrated Calcium Chloride. $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$

Source.—May be obtained by neutralising hydrochloric acid with calcium carbonate, and crystallising the product. Contains 98 to 102 p.c. Hydrated Calcium Chloride.

Characters.—Colourless crystals; odourless; taste, slightly bitter. Very deliquescent. Soluble in 0·25 part of water, and in 0·95 part of alcohol (90 p.c.).

B.P. Dose.—By intramuscular injection :—1 to 3 grs. or 0·06 to 0·2 gm. By intravenous injection :—10 to 30 grs. or 0·6 to 2 grms.

CALCIUM GLUCONAS

Calcium Gluconate. (Calc. Glucon.). $\text{C}_{12}\text{H}_{22}\text{O}_{14}\text{Ca} \cdot \text{H}_2\text{O}$

Source.—It is the normal calcium salt of gluconic acid. Contains 99 to 104 p.c. Calcium Gluconate and 8·9 p.c. of Calcium.

Characters.—A white, crystalline or granular powder; odourless, tasteless. Soluble in 30 parts of water at 25°C., in about 5 parts of boiling water; insoluble in dehydrated alcohol, in ether, and in chloroform.

B.P. Dose.—30 to 60 grs. or 2 to 4 grms.

CALCIUM LACTAS

(Calc. Lact.)

Calcium Lactate. $\text{Ca}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 5\text{H}_2\text{O}$

Source.—Obtained by neutralising diluted lactic acid with calcium carbonate, and evaporating the resulting solution.

Characters.—A white, almost tasteless powder. *Soluble* in 18·5 parts of water. Readily soluble in hot water. Forms a clear colourless solution.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

CALCIUM PHOSPHAS

(Calc. Phosph.)

Calcium Phosphate. $\text{Ca}_3(\text{PO}_4)_2$

Source.—Obtained by the interaction of calcium chloride and sodium phosphate in the presence of ammonia.

Characters.—A light, white, amorphous powder. No odour or taste. *Solubility*.—Insoluble in water.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grms.

NON-OFFICIAL PREPARATIONS

1 *Syrupus Calcii Lactophosphatis, B.P.C.*—Calcium lactate 75 g_m, concentrated phosphoric acid 29 mls, sugar 700 g_m, triple orange flower water 25 mls, water q s to 1000 mls. *Dose*—30 to 60 ms. or 2 to 4 mls

2 *Calcium Lævulinate, Syn—Calcium Lævulic*—Contains 1483 p c Ca. A stable and very soluble salt, easily assimilable. *Dose*—For intramuscular

injection, 2 ml of 20 p c solution for *intravenous injection*, 5, 10 or 20 ml of 18 p c solution

3 *Calci et Sodii Lactas*, B.P.C.—Occurs as white powder or as colourless, hard granules. Deliquescent. Soluble in 15 parts of water. Action same as other calcium salts, but is more soluble and easy of absorption. Specially useful in *night sweats of phthisis*, *hemoptysis* and *difficult dentition*, and in certain types of *dermatitis*. Dose—5 to 30 grs or 0.3 to 2 gm

PHARMACOLOGY AND THERAPEUTICS

Calcium is an important constituent of the animal body, and it is to the large proportion of calcium phosphate which it contains that the body skeleton owes its most essential property of rigidity. It is present to a considerable amount in all soft tissues and the blood, and is essential to most forms of living matter, and for the activity of certain ferments. Thus the milk will not curdle, nor the blood will coagulate, in the absence of calcium. Important as it is to the body mechanism, provision is made for its supply, and calcium is present in both animal and vegetable foods, although vegetable foods are much richer in calcium than the foods of animal origin. Milk and yolk of eggs are specially rich in calcium in a readily assimilable form. The young animal therefore is freely supplied with calcium at a period of life when it is necessary for its growth. Deficiency of calcium in food, therefore, has a prejudicial effect on the growing animals, owing to the larger amount of calcium necessary for the growth of the skeleton during this period, although very little untoward effect is observed in grown up animals.

The changes following calcium starvation resemble those observed in rickets in children. In rickets, however, the softness of the bones is not due to any deficiency of calcium in the food, but to lack of sunlight and vitamin D, which promote the absorption of calcium and phosphorus in balanced proportion, so that lime is not deposited on the bones. Therefore administration of calcium does not improve rickets.

Another condition which resembles rickets of children is sometimes observed in women during the period of pregnancy and lactation. Owing to the excessive demand of the growing child, the mother's skeleton becomes depleted of calcium which becomes soft and spongy, unless this demand is met by proper supply of calcium. This condition is known as osteomalacia, and like rickets is due to deficiency of vitamin D, lack of sunlight and derangement of calcium metabolism.

Calcium is present in all tissues, and not only the heart but other tissues of the body are sensitive to disturbances in the amount of calcium and sodium in the blood. Given intravenously in large doses, lime salts lessen the irritability of the cerebral cortex, while deficiency of the calcium in the

blood causes increased irritability of the brain with muscular twitchings.

An intravenous injection of chloride in non-toxic doses in man is followed by flushing of the skin and face, a hot feeling over the whole body, constriction of the throat, and sometimes nausea and vomiting. The peripheral vessels dilate and the systolic pressure falls. The heart becomes slow from **vagus stimulation** which is antagonised by atropine, the action resembling digitalis in some respects. Soon, however, the rate becomes normal and even accelerated, and the blood pressure rises from stimulation of the sympathetic.

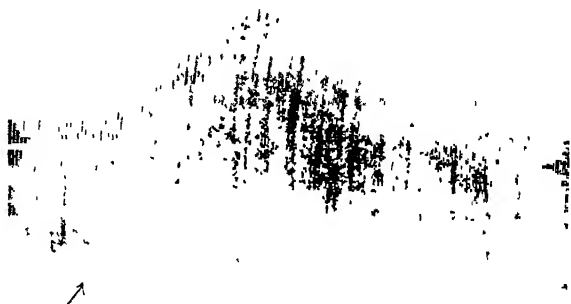


FIG. 2.—Movements of Isolated Rabbit's Heart perfused with Locke's Solution showing effect of Calcium.

At point of arrow a small amount of calcium chloride was administered.

On isolated heart calcium increases its muscular activity and tone, and acts as a tonic. It antagonises the depressant effect of potassium, and its absence stops rhythmic activity of other plain and striated muscles which reappears with increased tone on the addition of calcium. In cases of weakness of the cardiac muscle caused either by valvular insufficiency or myocarditis, the addition of calcium to the digitalis treatment increases the optimum action of the latter.

The pupils are contracted from direct stimulation of the sphincter, and probably from partial stimulation of the nerve ending. This is followed by dilatation from sympathetic stimulation.

All the above effects are elicited by the intravenous injection, and are not so marked when administered by the mouth, due to slow absorption. Calcium antagonises the effect of magnesium and potassium (see page 68).

The normal calcium requirement of an adult is about 0.45 grm. daily. During the growing period, pregnancy and period of lactation the demand is greater. It is absorbed

with difficulty and it has been estimated that only 60 p.c. of calcium of the food is absorbed. Therefore 1 gm of calcium must be taken daily with food to supply the adequate requirement. One litre of fresh cow's milk contains 1 gm of calcium.

Whether given in soluble or insoluble form, calcium is absorbed with difficulty. Its absorption depends upon the nature of the intestinal contents. During the digestive period the reaction of the upper part of the gut is frequently on the acid side and absorption of calcium takes place in the form of acid calcium phosphate. If the contents of the intestine be alkaline, calcium is precipitated as insoluble carbonate or phosphate, and deficiency of vitamin D renders the gut contents more alkaline and therefore retards absorption. If the intestine contains unsaturated fatty acids as derived from cod-liver oil, butter or bacon fat, calcium forms soluble soap and is readily absorbed. Calcium salts of fatty acids though insoluble are absorbed as soluble calcium salts possibly due to their solubility in bile. Calcium metabolism is regulated by ultra-violet rays, and Fussball* has shown that on a less calcium diet, as compared to controls, irradiated rats showed distinctly better calcium deposition, growth and increased calcium content of the serum.

Calcium is essential to the process of normal coagulation of the blood, which may be prevented by precipitating it by oxalates, citrates, and fluorides. It is also necessary for the action of thrombokinese or for the conversion of prothrombin into thrombin. Administered *per os* calcium has no appreciable effect in increasing the calcium content of the blood. Given intravenously or subcutaneously, the calcium content of the blood may remain high for a short time, the strength and duration depending not only upon the amount of calcium given but also on the calcium content of the blood. It is, however, used in purpura, aneurism, hæmophilia, hæmoptysis and other internal hæmorrhages, and as a preventive before operation in persons suffering from jaundice, or subject to hæmorrhage. In these cases it is administered intravenously in 10 p.c. solution of the chloride, about 5-10 c.c. being introduced at a time. The gluconate solution being less irritant may be administered intramuscularly.

Calcium circulates in the blood partly in combination with proteins and partly as diffusible salt. Of the diffusible calcium the portion existing in an ionised form performs the important functions. The normal blood serum contains 9 to 11 mg. of calcium per 100 c.c. and this concentration is constant, and is regulated by the parathyroid hormone, calcium in the food, reaction of the tissues, and vitamin D. In tetany following parathyroidectomy the calcium content

**American Journal of Physiology*, 1928.

of the blood is diminished, sometimes falling as low as 5 mg. per 100 c.c., and the symptoms following parathyroid-ectomy or of tetany may be checked by restoring the blood calcium level to normal by the use of large doses of calcium, or by the injection of parathyroid hormone, or by measures which increase the acid balance of the body, *e.g.* acids, ammonium chloride or calcium chloride, which cause acidosis. It has been shown that the acid-balance determines the concentration to which the plasma can hold calcium in solution. Conversely any change in the reaction of the blood towards alkalosis decreases the amount of *functioning* diffusible calcium without altering the calcium content. In tetany and spasmophilia of children following rickets, good results are obtained by the use of large doses of calcium which **depress nervous excitability**. The chief point is to cure rickets when the symptoms of spasmophilia will disappear. Since parathyroid increases the serum calcium at the expense of the calcium of the bones, which are already deficient, the use of parathyroid is contra-indicated in rickets (*see* Parathyroid). It may be used in chorea, a disease characterised by low total serum calcium content with corresponding diminution of the calcium content of the cerebro-spinal fluid.

The soluble lime salts increase the resistance of the red blood cells to certain hæmolytic serums and also lessen the liability to **anaphylactic reaction** in sensitive persons. They are of great value in **bronchial asthma** where they increase the sympathetic excitability in cases with evidence of vagotonia; and are also useful in hay fever, acute rhinitis, serum disease, and other conditions attended with parasympathetic excitability. It is used in **pleural effusions** on the hypothesis that there is a disturbance of the calcium-sodium balance in the tissues, there being a comparative deficiency of the former and corresponding increase of the latter.

Owing to the constant demand on the part of the growing fœtus for calcium, the serum calcium of the mother becomes low, and administration of calcium during pregnancy and the period of lactation protects the mother from calcium deficiency by maintaining the calcium at its proper level.

It is largely used nowadays in **pulmonary tuberculosis** on the assumption that the healing of tubercular lesions in the lungs is associated with calcification and that there is excessive excretion of calcium in this disease. There is however no reason to believe that there is any deficiency of serum calcium in this disease, and clinical results are not unanimous. In a certain number of cases a temporary benefit is observed as it reduces the temperature, improves the appetite, checks night sweats, and helps the patient to gain in weight. In intestinal tuberculosis it is used with better results in early cases, but is of no use in severe forms,

although it is worthy of a trial. Owing to the deficiency of calcium, its use has been suggested in **sprue** either alone or with parathyroid.

Calcium is useful in **lead poisoning** as it causes elimination of lead from the body by increasing the exchange of calcium and lead between the bones and the blood. During acute attacks it helps storage of lead in the bones and the lactate is given in 30 gr doses three times a day, or a 5 p.c. solution of chloride or gluconate intravenously. After the acute stage, slowly mobilise the stored lead by low calcium intake and by producing acidosis. It has some protective action on the liver and its administration prevents damage to the liver caused by carbon tetrachloride.

One of the important specific actions of calcium is its power to retard inflammatory process, and that transudation and œdema are favoured by withdrawal of calcium, which normally serves to check the permeability of the vessels. Calcium is therefore used in serous headaches, angioneurotic œdema, urticaria, chilblains, and conditions suggesting abnormal permeability of vessels, but with doubtful results.

The chloride increases the acidity of the urine, as quite a large part of calcium is converted into carbonate and escapes absorption, the liberated chloride is absorbed and increases the proportion of fixed acids in the body causing acidosis. It is a powerful diuretic due to increase of non-colloidal constituents of the blood. It has been used in acute and subacute nephritis where the liberated chloride ions combine with sodium and are excreted as sodium chloride with large amount of water (Cushny).

To promote **nutrition and cell growth**, the phosphate is exceedingly useful in the case of children who have overgrown their strength; in women weakened by child bearing, prolonged suckling, or excessive menstruation; in anæmia and exhaustion brought about by prolonged suppuration diarrhœa, leucorrhœa, etc.

The phosphate is also used to expedite the union of fractures and the healing of caries of bones

Excretion of calcium takes place through the intestine mainly (about 75 p.c.) and less with the urine, depending upon whether it forms a soluble or insoluble salt in the intestine. If it forms an insoluble phosphate it is excreted with the stool, whereas if it forms a soluble chloride it is mainly excreted with urine.

Prescribing hints—Calcium is best given in solution after food. But as all lime salts are feebly absorbed we are doubtful as to the wisdom of giving them in excessive doses as they may derange the stomach. The objection to the use of chloride is the taste. But this is noticed only when concentrated solutions are used. For the treatment of tuberculosis it is given intravenously for prolonged periods in 5

to 10 p.c. solutions; commencing with 2 c.c. and then working up to 10 c.c. Given subcutaneously, or when it leaks into the tissues during intravenous administration, local inflammation and necrosis result, but gluconate does not. For its diuretic effect the chloride is given in large doses (30 to 40 grs.), three or four times a day. Given intravenously the effects are quicker and more definite than oral administration. In urgent cases therefore it should be given intravenously in doses of 0.25 grm. in 5 c.c. of water. Ordinarily intramuscular injection gives just as good results and the gluconate is used for the purpose. The action of the lactate is somewhat weaker and therefore larger doses are required. Calcium should not be used intravenously simultaneously with digitalis as it may cause fatal results.* Calcium should not be prescribed with carbonates, sulphates, or sp. ammon aromat. which will throw insoluble precipitates

CALCIUM HYDROXIDE

Calcium Hydroxide. (Calc. Hydrox.). $\text{Ca}(\text{OH})_2$

Syn.—Calcii Hydras; Slaked Lime. Syn. I.V.—*Chun*, Beng. *Chunam*, Hind.

Source.—Freshly prepared by the action of water on lime. Contains not less than 90 p.c. Calcium Hydroxide.

Characters.—A soft, white alkaline powder. *Solubility*.—Slightly soluble in water; more freely in solutions of glycerin and of sugars.

Incompatibles.—Vegetable and mineral acids, and metallic salts.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

OFFICIAL PREPARATION

1 *Liquor Calcii Hydroxidi*. Syn.—*Liquor Calcis*; *Lime Water*.—0.15 p.c. w/v of calcium hydroxide. A clear, colourless liquid with alkaline taste. Absorbs CO_2 from the air and forms a film of calcium carbonate on the surface. B.P. Dose.—1 to 4 oz. or 30 to 120 mls.

PHARMACOLOGY

Externally—Unslaked or slaked lime is a caustic, but its action is localised. Lime water is a local sedative and astringent when applied to the broken skin.

Internally. **Alimentary canal**—The chief action of the oxide and hydroxide is due to the alkalinity and not to the calcium. Like chalk, lime water neutralises free acids of the contents of the stomach and acts as an antacid, but more powerfully. It makes the curd of milk more flocculent. It has a slight sedative property. In the intestine it is an antidote for poisoning by mineral acids, oxalic acid and zinc chloride.

THERAPEUTICS

Externally—As a caustic in the form of Vienna Paste (see page 69), slaked lime may be used to destroy warts and

*Mengle, *Jour Amer Med Assoc*, 1, 1936

small epithelial and other growths. Lime water, either with linseed oil (Carron oil), olive oil or glycerin is a soothing application to burns and scalds. An addition of 1 to 2 p.c. of phenol increases its efficacy. It makes a soothing astringent dressing for weeping eczema, and may be used as an injection to lessen the discharges in leucorrhœa, gonorrhœa, gleet, otorrhœa, etc., even when inflammation is present.

Internally. **Alimentary tract**—It is chiefly used as a diluent for milk to make the curd more flocculent (1 in 3 or more), and to check vomiting of infants. In the same way it may be given in enteric diarrhœa and other affections to prevent the milk from forming hard indigestible lumps, but its use has now been replaced by sodium citrate. As an astringent it is useful in mild infantile diarrhœa.

Prescribing hints—Lime water is ordinarily given in milk. To suckling babies one teaspoonful with an equal quantity of milk may be given every 3 hours before nursing, and to hand-fed ones a dessert-spoonful in each bottle.

AGNESII OXI UM LEVE

Light Magnesium Oxide (Mag. Oxid. Lev.)

Syn—Magnesia Levis; Light Magnesia

Source—Prepared by heating light magnesium carbonate to a dull red heat

Characters—A very light, white powder; odourless; taste, slightly alkaline. Almost insoluble in water

B P Dose—10 to 60 grs or 0.6 to 4 grms

OFFICIAL PREPARATION

1. **Mistura Magnesi Hydroxidi** *Syn*—*Cream of Magnesia*—Contains 8.25 p.c. w/v of magnesium hydroxide, or 12.5 grs. of magnesium oxide in 240 ms. *B P Dose*—60 to 240 ms or 4 to 16 mls

MAGNESII XIDU P N ER SUM

Heavy Magnesium Oxide. (Mag. Oxid. Pond.)

Syn—Magnesia Ponderosa; Heavy Magnesia

Source—Prepared by heating heavy magnesium carbonate to a dull red heat.

Characters—A white powder; almost insoluble in water, but readily dissolved by acids. Insoluble in alcohol (90 p.c.). Odourless; taste, slightly alkaline

Incompatibles—All acids.

B P Dose—10 to 60 grs or 0.6 to 4 grms

AGNESII CAR NAS LEVIS

Light Magnesium Carbonate (Mag. Carb. Lev.)

Source—Prepared by boiling together *dilute* aqueous solutions of magnesium sulphate and sodium carbonate.

Characters.—A light, white powder. Odourless; almost tasteless. *Solubility*—Almost *insoluble* in water, insoluble in alcohol (90 p.c.); soluble in dilute acids with effervescence

B.P. Dose.—10 to 60 grs. or 0·8 to 4 grms.

Enters into.—Pulv. rhei co

MAGNESII CARBONATIS

Heavy Magnesium Carbonate. (Mag. Carb. Pond.)

Source.—Prepared by mixing boiling concentrated solutions of magnesium sulphate and sodium carbonate, evaporating to dryness, and washing the product.

Characters.—A white, granular powder; odourless and tasteless. Almost *insoluble* in water, and in alcohol (90 p.c.); soluble with effervescence in dilute acids.

B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

Enters into.—Pulv. rhei co, Troch. bism. co

OFFICIAL PREPARATION

1. *Liquor Magnesii Bicarbonatis*. *Syn*—*Fluid Magnesia*.—7½ grs. in 1 oz. A clear, colourless liquid, may effervesce when the bottle is first opened. B.P. Dose.—1 to 2 ozs or 30 to 60 mls.

NON-OFFICIAL PREPARATIONS

1. *Magnesium Trisilicate* *Syn*—“*Magnosorbent*”—A white amorphous insoluble powder, prepared by mixing solution of magnesium sulphate and sodium silicate. Valuable antacid and adsorbent. *Dose*—5 to 30 grs or 0·3 to 2 gm

2. *Mistura Alba*, B.P.C.—Mag Carb Lev 400 grs, Mag Sulph 5 ozs, Peppermint Water to 20 ozs. *Dose*—½ to 1 oz or 15 to 30 mls as an aperient

3. *Liquor Magnesii Citratis*, B.P.C. *Syn*—*Lemonade Purgative*—Heavy Magnesium Carbonate 40 G, Acid Citric 90 G, Syrup of Lemon 160 mls, Pot. Bicarb 75 G., Water to 1000 mls. A pleasant refrigerant draught and saline aperient. *Dose*.—3 to 10 oz or 100 to 350 mls

4. *Red Mixture* (Dr Goodeve's)—Mag Carb Pond 30 grs, Rhubarb 10 grs, Sp Ammon Aromat 30 ms, Ol Anisi 2 drops. Water to 2 ozs Mix. *Dose*—One teaspoonful every 3 or 4 hours till bowels operate

MAGNESII SULPHATIS

(Mag Sulph)

Magnesium Sulphate. $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$

Syn.—*Epsom Salts*.

Source.—Prepared by the interaction of magnesium carbonate and sulphuric acid. Contains 99·5 and not more than the equivalent of 102 p.c of pure magnesium sulphate.

Characters.—Colourless crystals; odourless. Taste, cool saline and bitter. Effloresces in warm dry air. *Soluble* in 1·5 parts of water, sparingly soluble in alcohol (90 p.c.)

Incompatibles.—Potassium and sodium carbonates and bicarbonates, lime water, lead acetate, and tartarated soda which precipitates magnesium tartrate.

B.P. Dose.—30 to 240 grs or 2 to 16 grms.

Enters into.—Mist. sennæ co. and mist. mag. hydrox.

PHARMACOLOGY OF MAGNESIUM SALTS

Internally **Gastro-intestinal canal**.—Both the oxide and the carbonate are **alkaline**, and neutralise the normal or the excessive acidity of the stomach, and the oxide does this without inducing subsequent hypersecretion. The carbonate sets free carbonic acid, which exerts a local sedative influence and provokes subsequent hyperacidity. They act as

antacids. (Being sparingly soluble their antacid action extends down the intestine, where they are converted into soluble and therefore cathartic magnesium bicarbonate. What is unaffected is left insoluble. But the direct effect of magnesium ion is that of depression which is more marked when administered by the intravenous or intramuscular injection or applied to the excised strip of the intestine. (For action of Magnesium Sulphate, see Purgatives).

Blood—Magnesium salts enter the blood as a chloride or lactate and render the plasma more alkaline. If salines are used in concentrated form they draw fluid from the blood and tissues and render the blood more concentrated.

Nervous system.—Taken by the mouth, magnesium salts have very little systemic effect owing to their slow absorption and rapid elimination. The typical effects of Mg-ion are elicited when the salts are given either intravenously or subcutaneously. Magnesium acts as a narcotic and anæsthetic resembling chloroform, but unlike other hypnotics, it acts *indifferently* upon all parts of the central nervous system. Magnesium depresses the central and peripheral nervous system, and death takes place from paralysis of respiration. The heart is little influenced, the vagus remaining unaffected. It reduces the irritability of the intestine and counteracts the effect of physostigmine and barium. On the voluntary muscles it acts like curare. Injected into the spinal canal (5 c.c. of a 12 p.c. solution), or applied to the nerve trunks (25 p.c.), the sulphate induces anæsthesia resembling cocaine, but more lasting. All these symptoms are antagonised by the use of calcium salts intravenously, which restore the equilibrium between the various ions disturbed by an excess of magnesium.

Urine—What little salt is absorbed is passed out by the kidneys, increasing the flow of urine, rendering it alkaline, and to a certain extent dissolving uric acid; but the diuretic effect is weaker than that of the potassium and sodium salts. When given parenterally it is mostly excreted by the kidneys, almost the entire amount being eliminated within 48 hours.

THERAPEUTICS

Externally.—A saturated solution of magnesium sulphate used as a compress relieves pain and acts as a local anæsthetic and has been used in erysipelas, orchitis, arthritis and other inflammatory affections. Morrison recommends dressing of wounds with Magnesium Sulphate Paste made by mixing in a warm mortar dry magnesium sulphate $1\frac{1}{2}$ lbs., and 11 ounces of glycerole of carbolic acid (1 in 10). The dressing is left unchanged for three to eight days when profuse discharge of serum takes place, when more wool is used; subsequently a solution of the sulphate is used. This

acts by osmosis and draws fluid from the wound and prevents growth of aerobic and anaerobic organisms.

Internally.—The oxide, the carbonate and the silicate are largely employed as **antacid and adsorbent** in acid dyspepsia, heartburn, pyrosis, vomiting, sick headache, or any other complaint attended with acidity. Their antacid property is considerably increased by combining them with sodium bicarbonate and bismuth carbonate, as in the treatment of hyperacidity, gastric and duodenal ulcer and chronic gastric catarrh (see page 73). In all these conditions it should be given on an empty stomach in order that the insoluble salts may form a protective coating over the gastric mucosa and neutralise hyperacidity. As a tasteless, unirritating alkaline laxative, they are often used in combination with rhubarb, as pulv. rhei co., and Goodeve's "Red Mixture" in **constipation of children**. Liq. mag. bicarb. is an agreeable and alkaline laxative in acid dyspepsia accompanied by constipation.

As antidotes, magnesia is used in **poisoning by mineral acids, oxalic acid, and the salts of mercury, arsenic and copper**, as they form insoluble compounds with them. In **alkaloidal poisoning** they hinder the absorption of alkaloids by making the contents of the stomach alkaline. But in order to get these antidotal effects, they must be given in very large doses, which is the only objection. Magnesium sulphate acts as an antidote to lead and barium salts by precipitating their insoluble sulphates.

As a **diuretic** and feeble alkaliser of blood and urine, they are used in gout and gravel cases, where the salts of potassium and sodium are not well-borne. Many mineral waters containing magnesium are valuable diuretics, such as Harrogate, Carlsbad, Ems, Baden-Baden, etc.

For its paralysing effects on the nerve tissue the sulphate has been used as intraspinal injection in **tetanus** (3 to 4 c.c. of a 25 p.c. solution), and for the production of **spinal anæsthesia**. In tetanus it relieves spasms, but does not cure. Similarly intravenous injections of 10 to 25 mls (150 to 375 ms.) of a 10 p.c. solution have been used to relieve spasms of **eclampsia**. This is followed by 5 to 10 ms. of 25 p.c. solution intramuscularly after each convulsion, until controlled. It has also been used hypodermically in **chorea and epilepsy** and to relieve **intracranial pressure**, when concentrated solution has been used per rectum (3 to 6 oz. in water). In the treatment of **chorea** of children of 1 to 5 years, 3 to 5 ms. of a 25 p.c. aqueous solution is given as injection deep into the buttocks every 2 days, and for older children 10 ms. Improvement generally occurs after 2 to 5 injections. Because of its hypnotic property, it has been recommended (intramuscularly 0.25 G. per kilo) as a preliminary to ether anæsthesia, when it reduces the minimal

concentration of ether required to produce general anaesthesia. As an enema, or intravenously (2 c.c. of a 50 p.c. solution), it is valuable in headaches following spinal anaesthesia. The *margin of safety* between the effective therapeutic dose and the toxic dose being small this restricts its use, as it paralyses the respiratory centre when used in large therapeutic doses.

Note —For injection the solutions should be sterilised in an autoclave.

A II SULPHAS

Barium Sulphate. BaSO_4

Source —Prepared by the interaction of a soluble barium salt and a soluble sulphate.

Characters —A heavy, white, amorphous powder. No odour, or taste. Stable in air. *Insoluble* in water, slightly soluble in hydrochloric acid, and in nitric acid.

NON-OFFICIAL PREPARATIONS

1 *Pulvis Barni Sulphatis Compositus, B.P.C.* *Syn* —*Barium Meal, Shadow Meal* —Barium sulphate, 750, cocoa powder, 94, arrowroot, 94, compound powder of tragacanth, 31, sucrose in powder, 31, *Dose* —4 to 8 oz or 120 to 240 grm

2 *Barii Chloridum* —Colourless crystalline plates, soluble in $2\frac{1}{2}$ parts of water. *Dose* — $\frac{1}{2}$ to 2 grs or 0.03 to 0.12 grm. Maximum single dose 3 grs

ACTION AND USES OF BARIUM

Barium belongs to the group of alkaline earths but is more poisonous. The soluble salt (chloride) is absorbed with difficulty from the intestine but sufficiently to produce systemic effect. The chief action is exerted on all forms of muscular tissue which are powerfully stimulated. On the skeletal muscles the effects resemble those of veratrine, and since they are not antagonised by curara, it acts directly on the contractile substance. All the plain muscles are similarly affected, *e.g.* those of the intestine, bladder, vessels, and bronchi. Owing to the vaso-constriction it causes a rise of blood pressure. It increases the excitability of the heart, slows the rate and improves its tone, resembling digitalis effects; and at one time was suggested as a substitute for that drug. In practical therapeutics, however, it has not come up to the expectations made of it, although its use has been suggested in syncope of heart block.

Given by the mouth in large doses, the chloride causes nausea, vomiting, colicky pain and severe diarrhoea, tonic and clonic convulsions and death from paralysis of the central nervous system.

Sulphate of barium is insoluble and passes through the body unchanged, and being opaque to X-rays is used in preference to bismuth as a contrast meal in X-ray examination of the alimentary canal, either by the mouth or per

rectum. Two to 5 ounces are generally required, and are given mixed with cornflour, kaolin and malted milk, or in the form of *shadow meal*. Atropine ($\frac{1}{84}$ gr. or 0.001 G.) is a valuable adjuvant specially for visualisation of the appendix, for which object it is given as an enema one hour before barium. Barium however is inferior to bismuth, which, owing to its high molecular weight, gives a darker shadow.

Caution—As accidental deaths have taken place by the use of poisonous *barium sulphide* when the sulphate has been prescribed, the physician should be careful in writing the prescription in full, without abbreviation, and should satisfy himself before allowing the patient to take the drug. It is always safe to order some special preparation intended for X-ray examination only.

Baryta Sulphurata, B.P.C. *Syn*—*Sulphide of Barium*—It is a caustic and poison, and it is used as a depilatory to remove superfluous hairs, mixed with wheat starch in the proportion of 1 to 3. Make a paste with water and apply on the part and scrape off with a blunt knife after five to ten minutes.

GROUP II : ACIDS

Acid Acetic, Trichloracetic, Citric, Tartaric, Hydrochloric, Nitric, Sulphuric, Phosphoric, Hypophosphorous, Lactic, Boric (*see* Antiseptics), Hydrobromic (*see* Bromides)

ACI UM ACETICUM

Acetic Acid. (Acid. Acet.)

Source.—Prepared by the destructive distillation of wood, or by diluting glacial acetic acid. Contains 33 p.c. of acetic acid.

Characters.—A clear, colourless liquid with a pungent odour. Taste, sharply acid Sp. gr. 1.044-1.045.

OFFICIAL PREPARATIONS

1. **Acidum Aceticum Dilutum.**—6 p.c. of acetic acid Sp. gr. 1.008 B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

2. **Oxymel.**—15 p.c. B.P. Dose.—30 to 120 ms. or 2 to 8 mils

ACIDUM ACETICUM GLACIALE

Glacial Acetic Acid. (Acid Acet Glac.). CH_3COOH

Source.—Obtained by the action of sulphuric acid on an acetate, or by synthesis. Contains 99 p.c. of acetic acid.

Characters.—A clear, colourless liquid with pungent odour. Miscible with water and most fixed and volatile oils Sp. gr. 1.055-1.058.

Enters into.—Lin. terebinth. acet.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Glacial acetic acid is a caustic and is therefore used for destroying corns and warts. It speedily vesicates, and may be used in those cases where cantharidin cannot be employed, but it causes much pain, and if not cautiously applied, may produce a nasty sore

Acetic acid destroys *tinea*, and is an effective application

for ring-worm. Vinegar, or diluted acetic acid is an external refrigerant, and may be used as a cooling lotion in cerebral congestion, sprains and bruises; and sponging with vinegar will reduce pyrexia and check excessive sweating.

Internally.—Dilute acetic acid allays thirst by increasing the salivary secretion, and may be used as a gargle (15 ms to 1 oz.) in cases where dryness of the mouth is a troublesome symptom.

After prolonged use it diminishes the number of red blood-corpuscles and therefore its employment in obesity is contra-indicated. As an internal refrigerant, it may be given in fevers, cholera, diabetes, Bright's disease, etc.

Acetic acid is excreted in the urine as a carbonate. Given in large doses it passes out unchanged.

ACI U M T I C L O ACETICU

Trichloroacetic Acid. (Acid. Trichloroacet.). CCl_3COOH

Source.—May be prepared by the oxidation of chloral with nitric acid. Contains not less than 98 p.c. of trichloroacetic acid.

Characters.—Colourless, very deliquescent crystals, or crystalline masses, with a characteristic pungent odour. *Soluble* freely in water (9 in 1), in alcohol (90 p.c.), and in ether. Should be kept in well closed containers.

PHARMACOLOGY AND THERAPEUTICS

Trichloroacetic acid is a caustic, less painful than nitric acid. A weak solution is useful in stimulating granulating surface and for washing wounds and ulcers, specially phagedænic ulcers of the cheek. As a caustic the pure acid liquefied with minimum of water is used in warts, and to cauterise venereal and other sores. Mixed with glycerin (1 in 2) it is used in chronic pharyngitis. It has proved successful in leiomyoma cutis. Growths in the bladder have been treated at the University Clinic, Berlin, with a freshly prepared solution applied directly on the surface of the growth by means of a catheter passed through a cystoscope. The solution is made by heating the crystals in a test-tube until they become fluid, and to each 5 c.c. of the solution is added 5 drops of glycerin. 20 to 30 drops being slowly passed through the catheter. To prevent recrystallisation it is placed in a glass of warm water before using. It forms a delicate test for albumin in urine. A few drops of saturated solution added to the urine slowly forms a white cloud at the junction of the two fluids.

ACI U CIT ICUM

Citric Acid. (Acid. Cit.). $\text{C}_6\text{H}_8\text{O}_7, \text{H}_2\text{O}$

Source.—Obtained from lemon juice, or may be prepared from glucose. Contains not less than 99.5 p.c. of Citric Acid.

Characters.—Large, colourless crystals, or a white powder; slightly hygroscopic in moist air, and slightly efflorescent in dry air; odourless. Taste, strongly acid. *Soluble* in less than 1 part of water, in 1.5 parts of alcohol (90 p.c.).

20 grs. of Citric Acid } will neutralise { 28.5 grs. of Pot. Bicarb.
in 1 oz. of water } { 24 grs. of Sod. Bicarb.
{ 15 grs. of Ammon. Carb.

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

ACI UM TA TA ICU

Tartaric Acid. (Acid. Tart). $C_4H_6O_6$

Source.—Prepared from potassium acid tartrate. Contains not less than 99.5 p.c. of hydrogen tartrate.

Characters.—Colourless crystals, or a white powder; odourless; taste, strongly acid. *Solubility.*—In less than one part of water, and in 2.5 parts of alcohol (90 p.c.).

Incompatibles.—Salts of calcium, potassium, lead, mercury, alkalies, carbonates and vegetable astringents.

20 grs. of Tartaric Acid } will neutralise { 27 grs. of Pot. Bicarb.
in 1 oz. of water } { 22 grs. of Sod. Bicarb.
{ 15 grs. of Ammon. Carb.

B.P. Dose—5 to 30 grs. or 0.3 to 2 grm.

Enters into.—Pulv. Efferv. Co.

PHARMACOLOGY AND THERAPEUTICS OF CITRIC ACID AND TARTARIC ACID

Internally.—These acids unite with the bases to form neutral salts, and when given in an effervescing form the liberated carbonic acid gas acts as gastric sedative, therefore effervescing mixtures are used to check nausea and vomiting. Because they stimulate salivary secretion, they are used as refrigerant drinks in the form of lemonade to allay thirst in fevers.

Both citric acid and tartaric acid are used in the preparation of effervescing draughts and mixtures.

When added to drawn blood citric acid retards clotting by combining with calcium and forming a non-ionisable salt. Given by the mouth no such effect is observed. They are converted into neutral salts in the alimentary canal and are oxidised after absorption, *e.g.* potassium citrate is converted into potassium carbonate, carbonic acid and water, thereby increasing the alkalinity of the plasma.

Urine.—They are eliminated as carbonates, thereby increasing the alkalinity of the urine, except when given in large doses when they escape unchanged.

ACI UM Y OC LO ICU

Hydrochloric Acid. (Acid. Hydrochlor.)

Syn.—Muriatic Acid Spirit of Salt.

Source.—Obtained by dissolving hydrogen chloride in water. Contains 32 p.c. w/w of HCl.

Characters.—A colourless, strongly acid liquid emitting white fumes; sp. gr. 1.158 to 1.168.

Incompatibles.—Lead and silver salts, alkalies and their carbonates.

OFFICIAL PREPARATION

1. *Acidum Hydrochloricum Dilutum*.—Contains 10 p.c. w/w of hydrogen chloride. Sp. gr. 1.045 to 1.052. B.P. Dose.—5 to 60 ms. or 0.3 to 4 mils

ACI UM NIT ICUM

Nitric Acid. (Acid. Nit.)

Source.—Prepared by the interaction of sulphuric acid and sodium nitrate; containing 70 p.c w/w of HNO_3 .

Characters.—A clear, colourless, acid liquid, emitting corrosive fumes; sp. gr. 1.42.

Incompatibles.—Alkalies, alcohol, carbonates, oxides, sulphides, oxidisable substances, iron sulphate and acetate of lead

NON-OFFICIAL PREPARATIONS

1 *Acidum Nitricum Dilutum*.—10 p.c by weight of hydrogen nitrate *Dose* —5 to 20 ms or 0.3 to 1.2 mils

2 *Acidum Nitro-hydrochloricum Dilutum*—Contains about 1.25 p.c. w/w of nitric acid and 13.5 p.c w/w of hydrochloric acid *Dose*—5 to 20 ms. or 0.3 to 1.2 mils

PHARMACOLOGY AND THERAPEUTICS

Externally.—Being a powerful caustic, strong nitric acid is employed to destroy chancres, warts, hæmorrhoids, phagedænic sores and the poison of venomous snakes and rabid dogs. Owing to the formation of nitro-derivatives of tyrosine it stains the skin yellow. Applied diluted (5 to 10 c.c. in a bowl of water) it hardens the skin and prevents excessive sweating. As a bath nitro-hydrochloric acid is useful in chronic hepatic congestion (*see* page 38).

Internally.—Hydrochloric acid being the normal acid of the gastric juice aids transformation of the pepsinogen into pepsin and helps digestion of proteins. In the duodenum, acids reflexly excite the flow of pancreatic juice and govern the production of the hormone secretin. Since the entrance of secretin into the blood stream stimulates the formation of bile, hydrochloric acid also acts as a cholagogue. These acids are therefore used in gastric disorders preferably with *nux vomica* or some bitter.* As a stomachic they are given freely diluted before meals. In fermentative dyspepsia due to the absence of the antiseptic action of the gastric juice, and in other conditions arising from a deficiency of the acid, they are given after food. Given towards the end of gastric digestion they are useful in intestinal catarrh and chronic diarrhœa. They are also used to reduce the alkalinity of the urine in phosphatic deposits and to stimulate the hepatic action. Owing to the deficiency of the normal gastric juice so common in pernicious anæmia, hydrochloric acid has been largely used in its treatment in 20 to

*R

<i>Acid. Hydrochlor. Dil.</i>	ms	15
<i>Sp. Chlorof.</i>	ms.	15
<i>Tinct Nuc Vom.</i>	ms	10
<i>Inf Gent Co. Rec</i>	ad oz	1

30 ms. doses, freely diluted. For the same reason it is used in typhoid fever.

To avoid irritation of the throat and stomach, acids should be given freely diluted, and taken with a glass tube or quill to prevent their action on the teeth.

Acids are contra-indicated in catarrhal conditions of the stomach with excessive accumulation of mucus. Prolonged administration in large doses even in normal individuals causes irritation and indigestion.

ACI UM P OSP O ICUM

Phosphoric Acid. (Acid. Phosph.)

Source—Obtained by the oxidation of phosphorus in contact with water. Contains 89 p.c. w/w of H_3PO_4 .

Characters.—A colourless, syrupy liquid; taste and reaction acid; sp. gr. 1.75. Miscible with water.

Incompatibles.—Alkalies, carbonates, ferric chloride, lead salts and calcium salts.

OFFICIAL PREPARATION

1. **Acidum Phosphoricum Dilutum**.—10 p.c. w/w of phosphoric acid. B.P. Dose.—5 to 60 ms. or 0.3 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The diluted acid is a refrigerant and gastric tonic. It does not derange the digestion. It makes an agreeable drink in diabetes and febrile diseases. By some it is considered serviceable in cases of hypo-phosphaturia. It has no virtues of free phosphorus.

ACI UM YPOP OSP O SUM ILUTUM

Dilute Hypophosphorus Acid. (Acid. Hypophosph. Dil.)

Source.—May be prepared by the interaction of barium hypophosphite and dilute sulphuric acid. Contains 10 p.c. w/w of H_2PO_2 .

Characters.—A clear, colourless liquid; odourless; taste, strongly acid. Miscible with water, and with alcohol (90 p.c.).

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Uses.—It has the same action as other acids and being a powerful reducing agent is added to Syrupus Ferri Iodidi as a preservative. It is largely used in the form of hypophosphites, or as Syr. Hypophosph. Co.

ACI UM SULP U ICU

Sulphuric Acid. (Acid. Sulph.)

Source.—Obtained by the oxidation and hydration of sulphur dioxide. Contains not less than 95 p.c. w/w of H_2SO_4 .

Characters.—A colourless, corrosive, oily, acid liquid, evolving heat when water is added. Sp. gr. 1.84.

Incompatibles.—Alkalies and their carbonates, lead, silver, barium, calcium and strontium salts

OFFICIAL PREPARATION

1. **Acidum Sulphuricum Dilutum**.—10 p.c. Sp. gr. 1.064 to 1.073. The acid must be added to the water. B.P. Dose.—5 to 60 ms. or 0.3 to 4 mls.

NON-OFFICIAL PREPARATION

1 *Acidum Sulphuricum Aromaticum* *Syn.—Elixir of Vitriol*.—Sulphuric acid 70 mls, tincture of ginger 250 mls, sp cinnamon 15 mls, alcohol (90 p c) to 1000 mls *Dose* —5 to 20 ms or 0.3 to 1.2 mls

PHARMACOLOGY AND THERAPEUTICS

Concentrated sulphuric acid has a strong affinity for water and is a powerful irritant and caustic. Freely diluted it is used as a drink to allay thirst in cholera and as a mild hæmostatic to check gastric and intestinal hæmorrhage. It is eliminated by the kidneys and the bowels as a sulphate. Dilute acid or the Elixir of Vitriol is largely used in the treatment of diarrhœa and cholera.

It prevents absorption of lead by forming an insoluble sulphate, and therefore lemonade made with sulphuric acid is largely used by workers in lead factories as a prophylactic against plumbism.

GENERAL PHARMACOLOGY OF ACETIC, CITRIC, TARTARIC,
HYDROCHLORIC, NITRIC, PHOSPHORIC, HYPOPHOS-
PHOROUS, AND SULPHURIC ACIDS

Externally.—All these acids owe their property to the presence of hydrogen-ion. They neutralise alkalis, have a strong affinity for water, and in concentrated solution coagulate proteins. Acid solutions check the automatic movement of plain muscles and diminish the height of contraction to electrical stimulation of the striped muscle. These effects on isolated organs are proportional to their power of dissociation, and can be checked by neutralising the acid by an alkali. Acids are therefore protoplasmic poisons. The hydrogen-ion in organic acids, *e.g.* citric acid, is less dissociable, these acids are therefore less powerful than the inorganic acids, where the hydrogen-ion is easily dissociated.

In concentrated form acids are powerful irritants and caustics, and by penetrating into the skin and subcutaneous tissues cause severe pain and necrosis, and if extensive, produce symptoms of shock and collapse. Hydrochloric acid is less destructive, while concentrated organic acids are still less so, but may cause blisters and are only caustics. Dilute solutions, specially sulphuric acid, are local astringents and styptics. The organic acids freely diluted act as refrigerants and anhydrotics.

Internally. *Alimentary canal*.—The corrosive action of the concentrated acids is more marked when applied to a mucous surface. Thus when swallowed they cause severe burning and destruction of the mucous membrane of the mouth, œsophagus, stomach, etc., followed by severe shock, collapse and death. Recovery rarely takes place, but it is

always accompanied by contraction due to cicatrix formation, difficulty in deglutition and eventually death from inanition

Diluted acids have a peculiar sour taste and are mild astringents. They soften the enamel of the teeth and reflexly increase salivary secretion and allay thirst. In the stomach they neutralise free alkali and form neutral salts. Since pepsin acts in the presence of free acids, acids, specially hydrochloric acid, play an important part in the digestion of proteins. Acids also act as an antiseptic. The presence of free acid in the stomach increases pyloric peristalsis, closes the cardiac and opens the pyloric sphincters, while its presence in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. Excessive acidity therefore by retarding neutralisation in the duodenum delays opening of the pyloric sphincter and prolongs the period of digestion in the stomach. Acids also help the formation of secretin which in its turn increases pancreatic secretion.

Blood and tissues.—Acids are rapidly absorbed and circulate as salts formed by neutralising the alkalies of the body. They therefore reduce the alkalinity of the blood, and if the acids are absorbed in large quantities, sufficient to neutralise the fixed alkalies of the body, the alkalinity of the blood is so reduced that the animal dies of acidosis. This however is only possible in herbivorous animals, while in carnivorous animals and in man, the fixed alkalies are spared by the neutralisation of the acids by ammonia (see Acidosis).

Kidneys.—Acids are eliminated as neutral or acid salts, and as a result of salt action act as diuretics. But the urine is rendered more acid from the formation of acid salts which may cause irritation of the kidney and the genito-urinary mucous membrane. Nitric acid is partly converted into ammonia and tends to increase the alkalinity of the blood. The organic acids, viz. acetic, citric and tartaric, are oxidised in the body into carbonates and make the urine alkaline

Acute toxic action.—All these acids are irritant poisons. If swallowed in a concentrated form, intense burning pain extending from the mouth to the stomach, excoriation, and formation of grey or yellowish eschar in the mouth, severe abdominal pain and tenderness, vomiting of coffee-coloured matter containing dark clots of blood and shreds of mucus, constipation, or if bowels are open, stools dark from the admixture of blood are the prominent symptoms. Dyspnoea due to laryngeal swelling, either from irritant fumes or from the introduction of some of the acid, is not infrequent. Collapse with cold perspiration soon sets in and the patient dies.

Antidotes.—No pump. Alkalies, such as lime water, magnesia in a moderately diluted solution, or soap. Demulcents, as egg albumin, bland oils, linseed tea, etc. Morphine subcutaneously to relieve pain; etc.

ACIDUM LACTICUM

(Acid Lact.)

Lactic Acid. $\text{CH}_3\text{CHOH.COOH}$

Source.—Obtained by the lactic fermentation of sugar.

Characters.—A colourless, syrupy liquid; hygroscopic, inodorous; sp. gr 1.21. *Solubility*.—Freely in water, alcohol (90 p.c.), and ether.

B.P. Dose.—5 to 20 ms. or 0.3 to 1.2 mils.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The concentrated acid is **corrosive** and is used alone or in the form of a paste with kaolin to destroy lupus. A lotion (1 p.c.) is used to wash abscess cavities. Because of its low toxicity, it is used as a mild antiseptic and caustic for mucous surfaces, and a 10 p.c. solution is used as a douche in leucorrhœa; while in the form of a jelly or pessary containing 1 to 2 p.c. of the acid with boracic acid it is used as a **contraceptive**.

Internally.—A 10 to 50 p.c. solution in glycerin has been successfully applied to **pharyngeal tubercles** after scraping, the strength is slowly increased till pure acid is used. As a pigment or spray it is occasionally used to dissolve **false diphtheritic membranes**. On the stomach it acts like hydrochloric acid and is often given as a gastric adjuvant in dyspepsia. It allays thirst in diabetes and other diseases. Sour butter-milk may be used as a substitute for the same purpose. It is considered to be a valuable intestinal disinfectant, specially of the large bowel. It is useful in the diarrhœa of phthisis, of enteric fever, and in the green diarrhœa of infants. The usual practice is to give $7\frac{1}{2}$ ms. three times a day after food. Infants thrive better on milk to which lactic acid has been added in the proportion of 60 ms. to 1 pint. It enters the blood as a lactate, and is eliminated in the urine as a carbonate.

Soured milk at one time was very popular in the treatment of diseases of the large bowel, colitis, chronic dysentery, etc., and also in the summer diarrhœa of infants. To be free from danger the milk used must first be sterilised to get rid of all contaminating and undesirable organisms. To this sterilised milk some reliable preparation of lactic acid bacilli must be added, *e.g.* trilactin tablets or liquid trilactin, ferment lactyl, etc.; the vessel containing the milk is then covered and allowed to stand in a warm place, or a thermos flask may be used. After being thus incubated for from six to ten hours the milk is ready for use. From one to three pints may be taken daily. Cream, sugar, etc., may be added to render the preparation more palatable.

GROUP III

HEAVY METALS

The drugs belonging to this group have many properties in common, but individually they have some very important actions and therapeutic uses of their own. For instance, mercury is *antisyphilitic*, iron *hæmatinic*, while others are more or less *astringents* and *caustics*. In the form of pure metals they have practically no action, except a mechanical one, but become active only when they are capable of dissociation into ions. Iron and mercury are the only metals that are used in the pure form, all others are used either as organic or inorganic compounds. The more completely dissociated the ions of the salts are the more rapid and more intense is the action. Thus the inorganic salts are more active than the organic preparations and double salts, which are less readily ionised.

All the salts precipitate proteins and form albuminates of variable composition. In concentrated solutions the precipitate extends into the cells and may have an irritant or even a caustic effect, causing the death of the tissues. They are therefore *astringents*, *irritants* or *caustics*, according to the strength and preparation used. As a rule the acid ion is more important for the local action than the metal. The chlorides and nitrates are dissociated most rapidly and are *corrosives*, the sulphates are dissociated less readily and are less irritant, while the acetates, tartrates and citrates are least corrosives as they are very slowly dissociated. Of the different salts, lead and alum are *astringents*, perchloride and nitrate of mercury are *irritants*, and zinc, copper, silver are *irritants* or *astringents* according to the strength of the solution used.

The salts of the heavy metals are very slowly absorbed and slowly excreted, and are therefore more or less cumulative. Chronic poisoning by some of the metals may follow the repeated use for a long time even if the dose be very small. Mercury, however, is the only metal that is absorbed freely from the alimentary tract. Except mercury, excretion of these metals *via* the kidneys is less. They are mostly stored up in various organs, chiefly the liver, the spleen, the kidneys and the bone-marrow. In large doses they may produce nephritis. All are more or less *astringents*, and some, specially lead is constipating, while mercury is a purgative. The nervous system is sensitive to these metals. Disturbances of psychical centres, delirium, mania, peripheral neuritis, and sclerosis of the brain and cord are some manifestations of poisoning from heavy metals.

Many salts of heavy metals are powerful disinfectants,

perchloride of mercury is however extensively used as such. Their action is due to the precipitation of the proteins of the microbes, and a specific poisonous action on the bacteria themselves. The action of mercury is however complex; the metal is first adsorbed upon the surface of the bacteria and then enters and kills the bacteria. It therefore takes a longer time to act and will produce its germicidal action even in low concentration provided sufficient time is given. Naegeli has found that some metals in infinitesimal quantities kill algæ, infusoria and bacteria, which has been termed *oligodynamic action* of the drug. In practical therapeutics this oligodynamic action is produced by the colloidal metals. As these are not dissociated into ions they are not irritants, but the free ions present are pharmacologically active; although not powerful enough to produce any local irritation they have a powerful bactericidal effect in very dilute solutions.

Colloidal Metals.—Since the vital processes of the body fluids and living tissues are colloidal phenomena, it has been suggested that if therapeutic agents could be administered in colloidal form they will react with the body tissues where colloidal conditions prevail. A substance is said to be in colloidal state when its particles are sufficiently finely divided in sub-microscopic size as can be kept in solution without mechanical suspension. Colloidal solutions resemble true solutions in so far that the particles remain in suspension and do not form deposit as happens when a mechanical suspension is made. The particles in colloidal solution do not separate out in the liquid owing to Brownian movement and to the electric charges which they carry. In some this charge is positive, but in the majority it is negative, and the mutual repulsion of similarly charged particles keep them in suspension. Colloidal metal is obtained by passing an electric arc between metallic wires under water, when the metal remains evenly and permanently distributed in the solution in very fine subdivision. The metal exists in non-ionisable form and therefore does not cause any irritation, but becomes active by slowly passing to the ionic form by the action of bacteria. They have been credited of possessing certain properties in common with ferments.

The use of colloidal solutions in medicine is based on the fact that the minute particles remaining in solution give a larger surface area and therefore confer greater activity. Thus colloidal kaolin, owing to larger surface area, possesses a greater adsorptive power than ordinary kaolin. Colloidal metals have been extensively used as internal antiseptics in many forms of infections, chiefly puerperal and other septicæmias, but with doubtful results. Colloidal lead has been used in the treatment of cancer, and silver in the form of electrargol in septic conditions and infections. They are

used hypodermically and even intravenously. The injections are followed by a rise of temperature (sometimes hyperpyrexia) and leucocytosis. Their gradual transformation into the ionic form will elicit the typical action of the metal.

The heavy metals are classified as follows:—

- Class A: Antisyphilitic and antiseptic · **Mercury**
- Class B: Hæmatinic: **Iron**
- Class C: Astringents: **Lead, Silver, Zinc, Copper, Alum**
- Class D: Alternative: **Gold**
- Class E: Depilatory: **Thallium**

Of these **Mercury** will be discussed with other Chemotherapeutic Agents, and **Iron** with Drugs Acting on the Blood.

ASTRINGENT METALS

Lead, Silver, Zinc, Copper, Alum

PLUM I ACETAS

(Plumb Acet)

Lead Acetate. $\text{Pb}(\text{CH}_3\text{COO})_2 \cdot 3\text{H}_2\text{O}$

Syn.—Sugar of Lead.

Source.—Obtained by the interaction of lead oxide and acetic acid. Contains not less than 99·5 p.c. of pure lead acetate.

Characters—Small, white, monoclinic prisms, or heavy crystalline masses; slightly efflorescent; odour, acetous; taste, sweet, astringent. **Solubility.**—1 in 2·5 of water, 1 in 30 of alcohol (90 p.c.).

Incompatibles.—Mineral and tannic acids and their salts, alkalies, lime water, chlorides, iodides, preparations of opium, mucilage of acacia, albuminous fluids and hard water.

B P. Dose.— $\frac{1}{2}$ to 2 grs. or 0·03 to 0·12 grm.

OFFICIAL PREPARATION

1. **Suppositorium Plumbi cum Opio.** **Syn.**—*Suppositorium Plumbi Co.*—3 grs. of lead acetate and 1 gr. of opium in each.

LI QO PLUM I SU ACETATIS F TIS

(Liq. Plumb. Subacet Fort)

Strong Solution of Lead Subacetate

Syn.—Goulard's Extract.

Source.—Prepared by dissolving lead acetate in water, adding lead monoxide: filtering and washing.

Characters.—A clear, colourless alkaline liquid, becoming turbid from exposure; taste, sweet, astringent; reaction, alkaline. Sp gr. 1·28. Contains 19 to 21·5 p.c. of lead subacetate.

OFFICIAL PREPARATION

1. **Liquor Plumbi Subacetatis Dilutus.** **Syn.**—*Goulard's Lotion; Goulard Water.*—1·25 p.c. strong liquor.

PLUM I MONOXI UM

(Plumb Monox)

Lead Monoxide. PbO

Syn.—Litharge. **Plumbi Oxidum.** **Syn. IV.**—*Mudra sung*, Beng.

Source.—Prepared by the oxidation of molten lead.

Characters.—Pale brick-red, or pale orange, heavy scales or powder. **Solubility.**—In dilute nitric acid, acetic acid, in warm solutions of alkali hydroxides; almost insoluble in water.

Enters into.—The preparation of Liq. Plumb. Subacet. Fort.

OFFICIAL PREPARATION

1. **Emplastrum Plumbi.** *Syn.*—*Diachylon* or *Litharge Plaster*; *Emp. Plumbi Oleatis*, U.S.P.—A pale yellow solid, being a crude oleate, palmitate, and stearate of lead.

NON-OFFICIAL PREPARATIONS

1 **Pilula Plumbi cum Opio**, B.P.C.—Lead acetate 40 grs., opium 6 grs., syrup of glucose q s for 25 pills. *Dose*—1 to 2 pills

2 **Lotio Picis Carbonis et Plumbi**, B.P.C.—Solution of coal tar, 300 ms., strong solution of lead subacetate, 300 ms., distilled water, q s 20 oz

3 **Unguentum Plumbi Oleatis**, B.P.C. *Syn.*—*Diachylon Ointment*, *Hebra's Ointment*—Lead Plaster 50, Ol. Lavender (by weight) 1, Olive Oil (by weight) 49, melt with heat. Useful in *eczema*, excessive perspiration of feet and *sycosis*

ACTION AND USES OF LEAD MONOXIDE

The oxide has desiccant properties but it is scarcely ever used. *Emplastrum plumbi* is the basis of most of the plasters. It serves mechanically to hold the lips of *wounds* together, protects irritable surfaces, and by its pressure, helps the absorption of effused products or indolent enlargements.

PHARMACOLOGY OF LEAD SALTS

Externally.—Lead salts have a feeble action on the unbroken skin, but on the denuded surface and exposed mucous membrane, wound and ulcer, they produce precipitation of discharges and form an impervious coating on the surface. Since the metal contained in the precipitate has no destructive effect on the cells like mercury, it is not corrosive; on the other hand it has a sedative action and allays itching. It coagulates the albumin of the tissues. Lead therefore is an **astringent, antiphlogistic and local sedative**.

Internally—Insoluble lead salts have no taste, the soluble salts are astringent and sweetish. They have the same local action in the mouth, stomach and intestine as on the skin, and are converted into an albuminate and absorbed as such. The unabsorbed portion is eliminated by the stool as sulphide colouring it leaden black. They cause **constipation** and stop hæmorrhage from the intestine. The action is due to retardation of peristalsis and a diminution of secretion due to astringent action.

Absorption and elimination.—Lead salts enter the blood from the alimentary canal, skin, and the respiratory tract. Lead enters the blood more rapidly than any other heavy metal except mercury, and being excreted slowly, it is apt to accumulate in the body. Because of its slow absorption, large single doses do not produce any symptoms of poisoning, but minute doses slowly absorbed for a pro-

longed period give rise to symptoms of chronic poisoning. The central nervous system, kidneys, liver and the bone are the principal organs where it is deposited. It is excreted slowly by the urine, bile, sweat, milk and the fæces.

The action is best studied from cases of *chronic poisoning*.

The symptoms are characteristic, and involves the nutrition and the condition of the blood. Loss of appetite, nausea, impaired digestion, obstinate constipation, a sweet metallic taste in the mouth, intestinal colic (lead colic) and formation of a *blue line on the edges of the gums* are the early symptoms. The blue colouration is due to deposit of lead sulphide in the subepithelial tissue and cannot be removed by rubbing. This is formed when lead in circulation comes in contact with hydrogen sulphide formed by putrefaction around unclean and carious teeth, and does not occur if the teeth and mouth are kept clean.

Lead colic may sometimes be very severe, and is due to spasm of the intestine. The cause of this is not definitely known, although it has been suggested as being the result of direct action on the plain muscles, like the uterus. The contractions are not co-ordinated as happens in peristaltic movements, but result from spasmodic contractions of the localised circular muscles only. Therefore no purgation follows; on the contrary there is severe constipation. Some however hold that the contraction is due to vascular spasm, and is relieved by amyl nitrite.

Anæmia is common and is sometimes the only symptom. It may be due to malnutrition but mainly to destruction of red blood corpuscles, and the changes in red bone marrow are secondary to anæmia. A very characteristic condition of the blood is the appearance of *basophilic stippling*. There is an increase of leucoblastic cells with disappearance of fat, followed by gelatinous degeneration and atrophy. *Leucocytosis* is common.

The effect on the uterine muscle is responsible for *dysmenorrhœa*, *amenorrhœa*, *menorrhagia*, and abortion in pregnant women, and for this reason lead plaster is often administered with criminal intent. Peripheral vessels become powerfully constricted resulting in *arteriosclerosis* and high blood-pressure. This at one time was thought to be reflex from pain, but since it is permanent and remains after the subsidence of pain, which is spasmodic, it must be the result of direct action on the arterial muscle. In the same way the heart muscle is also affected although the actual amount of work done is not increased.

Severe cramps of the leg next appear followed by paralysis of the extensors of the forearm, leading to wrist drop from chronic peripheral neuritis of the motor nerves supplying the muscles. The affected muscles become the seat of fatty degeneration, but it is to be noted that the supinator longus escapes. The paralysis may extend to other muscles and there may be general paraplegia, and hemiplegia.

Arthralgia occurs in certain percentage of patients. The symptoms are sudden paroxysmal attacks of violent pains, generally at nights, and disturbed functions of joints and groups of muscles, specially those of the shoulder and the flexors. These attacks resemble gout and are possibly due to deposition of lead phosphate about the joints, or may be neuralgic, neuritic or central.

Occasionally marked cerebral symptoms are seen leading to lead *encephalopathy*. The onset may be gradual or sudden with vertigo, violent headache, tinnitus, strabismus and other cerebral manifestations like stupor, weakness and tremors. Saturnine lunacy and saturnine epilepsy may result from the action of the poison on the nervous centres. Also optic neuritis and blindness (lead amblyopia). This may be the sequence of albuminuric retinitis or effusion into the optic sheath.

As lead prevents excretion of urates from the blood, gouty inflammation of joints often ensues, specially in patients with a gouty diathesis. Chronic lead poisoning is also a common cause of granular kidney with all its attendant symptoms.

Tetra-ethyl of lead is now used with petrol, but gives rise to highly poisonous and toxic fumes. It is freely absorbed by the lungs and skin. The symptoms are the same as lead.

Treatment.—Conditions favouring calcium retention help storage of lead in the bones, and therefore calcium lactate, or milk (because of its high calcium content) should be given during the acute symptoms to help deposition of lead in the bone. After the acute symptoms are over efforts should be made to help excretion by maintaining a negative calcium balance by low intake of calcium, and by acid like phosphoric acid, or ammonium chloride. Atropine, morphine and nitrites to relieve colic and constipation. Potassium iodide to dissolve insoluble compounds of lead and magnesium sulphate to remove them from the system, and prevent their reabsorption after they have been eliminated into the intestine. Sulphur baths to help elimination by the skin; lumbar puncture in encephalopathy.

Acute toxic action.—Concentrated solutions of lead salts are irritant. Acute poisoning is rare, but has recently not been infrequently seen on account of the use of diachylon plaster as an abortifacient. Abortion certainly follows its administration, but acute plumbism leading to paralysis, blindness, insanity, and death also sometimes occur. Burning pain in the stomach, dryness of the throat, thirst, vomiting, colic, constipation with slate coloured stools, cold sweats, cramps in the legs, collapse; sometimes even stupor, coma, and convulsions are some of the symptoms induced by the acetate.

Antidotes.—Stomach-pump Zinc sulphate both as an emetic and antidote, followed by milk or the white of egg; dilute sulphuric acid. Calcium to help storage in the bones. Sodium and magnesium sulphate produce insoluble sulphates and open the bowels. Morphine or demulcent drinks to relieve colicky pain.

THERAPEUTICS OF LEAD SALTS

Externally.—Generally speaking, lead salts are useful in a variety of diseases:—(1) To *soothe irritation and control excessive discharge*, the lotions and ointments are employed in inflamed, painful, weeping eczema, irritable ulcers and wounds. The lotion may be used in vulvitis, leucorrhœa, otorrhœa, etc. A lead and opium lotion* is a good sedative application to bruises, sprains and other cutaneous inflammations. Diachylon ointment, alone or combined with zinc oleate or mercuric oleate ointments, makes a very effective non-irritant application. (2) To *allay irritation and itching*, a lotion or ointment is used in pruritus pudendi (the cause being first removed), urticaria, etc.†

Internally.—For its local astringent effects, Glycerinum Plumbi Subacetatis (strong solution of lead subacetate 5, glycerin 5, water q s), or a gargle can be used in tonsillitis, pharyngitis, etc. Lead acetate is the only salt that is used

*R

Tinct. Opii	ms 10
Liq plumb subacet. dil	ms 60
Aqua	ad oz 1

†R

Calamine	oz 3
Glycerin	oz 1
Liq plumb Subacet dil ad	oz 20

internally. Its chief use is to check severe diarrhœa and hæmorrhage from the stomach and bowels as in typhoid fever and tuberculosis. *Pilula plumbi c. opio* is a valuable preparation in such cases. Lead suppository or an enema of acetate of lead may be employed to arrest rectal hæmorrhages, and as an astringent in chronic dysentery.

Recently the use of colloidal lead in the treatment of cancer has been suggested by Blair Bell, but the treatment is still in its experimental stage and is attended with great risk of poisoning. Moreover, great care is required in the preparation of the compound and regulation of the dosage.

A GENTI NIT AS

Silver Nitrate. (Argent. Nit.). AgNO_3

Syn.—Lunar Caustic.

Source—Prepared by the action of nitric acid on silver.

Characters.—Colourless, tabular crystals. Taste, bitter, metallic.

Solubility.—In 0.5 part of water.

Incompatibles—Alkalies and their carbonates, bromides, chlorides, phosphates, iodides, acids (except nitric and acetic), alkaloids, and solutions of arsenic and tannin.

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{4}$ gr. or 0.008 to 0.016 gm.

OFFICIAL PREPARATION

1. **Argenti Nitras Induratus.** **Syn.**—*Toughened Caustic*—Greyish-white, or white cylindrical rods or cones. Freely soluble in distilled water and sparingly soluble in alcohol (90 p.c.). Obtained by fusing silver nitrate 95 parts and potassium nitrate 5 parts and pouring into moulds.

A GENTOP OTEINUM

Silver Protein. (Argentoprot.)

Syn.—Argentum-Proteinicum Forte; Strong Protein Silver; “Protargol.”

Source—It is a compound of silver and protein, and may be prepared by the action of a silver compound on gelatin in the presence of alkali. Contains 7.5 to 8.5 p.c. of Ag.

Characters.—A brown powder; odourless; somewhat hygroscopic. Slowly soluble in about 2 parts of water, forming a dark brown solution; almost insoluble in alcohol (90 p.c.).

N.B. It should be kept in well-closed container, protected from light, and the solution should be dispensed in amber-coloured bottles.

NON-OFFICIAL PREPARATIONS

1. **Argentum Colloidale** (Ciede's) **Syn.**—*Collargol*—Metallic silver in a colloid state. Its ointment (Argen. Coll. 15, Ceia Alba 10, Adep Benz 75) is used as a prophylactic to gonorrhœa and ophthalmia. **Dose**— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 gm. in pills or solution.

2. **Argentum proteinicum Mite**, U.S.P. **Syn.**—*Argyrol*, *Mild Protargin*—Silver rendered colloidal by the presence of, or combination with, protein. Contains 19 to 25 p.c. of silver. Dark brown or almost black shining scales or granules. Very soluble in water, but not in alcohol. An excellent non-irritating application for mucous membranes. In *colitis*, 1 p.c. solution as enema. For *cystitis*, use 1 in 5000 solution. As a mild caustic 1 in 100. In ophthalmic practice as a prophylactic against ophthalmia neonatorum 25 p.c. In gonorrhœa as a prophylactic, 10 p.c., urethral irrigation, 1 in 1000. Bowel wash, 0.1 to 1 p.c.

3 Albargum. *Syn.*—*Silver Gelatose*—Contains 15 p.c of silver. A 0.2 p.c solution useful as an injection in *gonorrhœa*. A 0.25 p.c solution as a bowel wash in dysentery.

PHARMACOLOGY OF SILVER SALTS

Externally.—Soluble silver salts unite chemically with the proteins of the tissues and discharges to form albuminates, but their action does not penetrate into the deeper tissues and is checked by sodium chloride which changes it into insoluble inert silver chloride. Applied to the unbroken skin in the form of a stick or in concentrated solution, it produces at first a white stain which soon turns black from exposure to light. The stain peels off as a dark scale if the application is light, or as a black slough if the application is prolonged. It is therefore an astringent and caustic.

It is an antiseptic but as soon as it comes in contact with any secretion of the body or with any tissue it is precipitated as inert silver chloride. The antiseptic action is due to its forming compound with proteins of the bacteria, but since it also combines with the proteins of the tissues there is irritation which is more marked when applied to delicate mucous membrane like the conjunctiva.

The protein compounds being non-ionisable are not precipitated and therefore are less irritant and feebly disinfectant. For the same reason the colloidal compounds are not corrosives nor irritants or astringents. They have no antiseptic action even after prolonged application, the antiseptic action depending upon the ionic concentration of the different compounds.

Internally.—In the mouth and stomach silver acts as an astringent. It has no astringent effect in the intestine as it is precipitated as silver chloride in the stomach and reduced to metallic silver in the intestine. Moderately large doses cause gastro-enteritis with collapse and death. Silver is not absorbed in sufficient quantity to produce any general effect, but if the administration is prolonged it is absorbed in very minute quantities, and the granules are deposited in the various parts of the body, chiefly the mouth and the gums, producing dark blue discoloration resembling lead poisoning. It causes a slate blue discoloration of the skin from deposition of the compound in all tissues of the skin except the rete Malpighi. This pigmentation or **argyria** is almost permanent. The same discoloration is also noticed in the conjunctiva from prolonged application of silver compounds and deposition of silver albuminate in the sub-epithelial tissue. The colouring sometimes spreads to the cornea when the vision is interfered with. This condition is known as **argyrosis** of the conjunctiva, and may be removed by the injection, after preliminary anæ-

thesia, of a solution of 12 p.c. sodium thiosulphate and 2 parts of a 2 p.c. solution of potassium ferrocyanide, with a fine platinum needle subconjunctivally.

Elimination.—Silver is excreted with the fæces as sulphide staining it dark brown, and by the intestinal secretion and bile. A portion is deposited in the kidneys and the liver.

Toxic action.—When given in poisonous doses the only symptoms produced are those of gastro-enteritis with vomiting and purging, extreme prostration, collapse and death. When given to animals the chief symptoms are those of central nervous system. They are paralysis of the vasomotor centre with fall of blood-pressure, disturbances of respiration and finally paralysis of the respiratory centre, general convulsion followed by paralysis beginning in the lower extremities. The heart is little affected; in fact it continues to beat even after the stoppage of respiration.

Antidotes.—In *acute poisoning* from accidental causes, mucilaginous drinks, such as thick gruel, should be immediately given to envelope the caustic; this should be followed by an emetic or stomach syphon. Common salt is the *chemical antidote*. White of egg, milk and water, and other demulcents may be given freely.

THERAPEUTICS OF SILVER SALTS

Externally.—Silver nitrate may be applied to exuberant granulations, callous, indolent ulcers, fistulæ, chancres, etc., because of its limited caustic and after-stimulating effects on them. It is a valuable caustic for post-mortem wounds, but not a reliable one for bites by poisonous snakes and rabid animals, as its action does not penetrate into the deeper layers. It arrests bleeding from leech-bites.

Eye and nose—A solution of silver nitrate (5 to 10 grs. in 1 oz.) is useful in granular conjunctivitis and ophthalmia neonatorum. As a preventive against ophthalmia neonatorum, both nitrate (1 to 2 p.c.) and argentoprotein are largely used, the latter up to 10 p.c. solution. The conjunctiva must first be rendered anæsthetic by means of cocaine. The silver solution is then applied with a camel-hair brush, and the excess of caustic afterwards neutralised by irrigation with normal saline solution. A weaker solution (1 to 4 grs. in 1 oz.) may be used as a collyrium in purulent conjunctivitis. A weak solution makes a valuable irrigation in rhinitis. Both protargol* and argyrol may be used in conjunctivitis as eye-drops; the former in strengths of 2 to 20 p.c., while the latter 25 p.c. A 10 p.c. ointment of argyrol may also be used.

Genitals.—Solid caustic is still used for cauterising granular or ulcerated os and cervix. A strong solution may be injected into or painted within the womb in endometritis or endocervicitis. A weaker solution (1 to 2 grs. in 1 oz.) makes an effective injection in gonorrhœa, leucorrhœa and

*R:

Argentoprot.	grs 10-20
Aqua dest.	ad oz. 1
Eye drop in conjunctivitis.	

pruritus pudendi due to leucorrhœa. Irrigation (1 in 1000 to 10,000) has been successfully used in many cases of gonorrhœa. Injections of protargol (1 in 500 or more) or argyrol are also useful. A 2 to 5 p.c. solution may be used to cauterise chancres and indolent ulcers. Being opaque to X-rays, collargol (20 p.c. solution) is injected into the ureter and renal pelvis for diagnostic purposes.

Internally. **Alimentary canal.**—Unhealthy or chronic ulcers in the mouth quickly heal after being touched with mitigated caustic. A solution (10 to 20 grs. in 1 oz.) is an excellent application for sore throat, acute or chronic, pharyngitis, follicular tonsillitis, and tubercular and other ulcerations of the larynx.*

It has been used in chronic diarrhœa, vomiting and in gastric ulcer without much benefit. As an enema (10 grs. to 1 pt.), it has been successfully employed in chronic dysentery and ulcerations of the bowel. Albargin 1 to 2 grains to 1 oz. makes an excellent bowel wash in cases of chronic bacillary dysentery and in colitic conditions. It should be used after a preliminary washing of the bowel with plain warm water.

Nervous system.—Silver was formerly largely used in many nervous diseases, specially epilepsy, but it is doubtful if any silver actually reaches the central nervous system, and the clinical experience has been disappointing. Moreover the unpleasant symptoms of argyria are the chief barrier to its use, and on this account nitrate of silver is now very rarely used by neurologists.

Caution.—To avoid argyria, the use of the drug must be suspended as soon as a dark line is noticed on the edges of the gums which may be removed by a course of acid tartrate of potassium, or potassium iodide. But perfect restoration to the normal does not occur. Its administration must be stopped for two weeks after two months' use, however small the dose may be. The use of hexamine has given good results in some cases.

Silver stains on linen can be removed by washing with a solution of potassium cyanide 3 gms., iodine 0.3 gm., and water 30 c.c. The stain on the skin may be removed (1) by potassium cyanide solution, but the part must be well washed afterwards, (2) by covering the skin with solution of iodine and then washing with a solution of sodium thiosulphate, or (3) by washing with corrosive sublimate (10 p.c.) solution.

Prescribing hints.—Silver salts are given in pills after food, but if their local action on the stomach is desired they should be given on an empty stomach, preferably in solution. For application to the skin, a solution of the nitrate in nitrous ether is the best, as it does not run in drops and is a stronger preparation than the aqueous solution. The ordinary silver preparations have been largely replaced by strong and mild argentoproteins and colloidal preparations.

*R

Argent nit.	grs 15
Aqua dest.	ad oz 1
Paint for sore throat, tonsillitis, etc	

✓ ZINCI C LORI UM

Zinc Chloride. (Zinc. Chlorid.). ZnCl_2

Source.—Obtained by the interaction of zinc and hydrochloric acid. Contains zinc, equivalent to not less than 95 p.c. of ZnCl_2 .

Characters.—Colourless, opaque, deliquescent rods or masses, or in granular powder; powerfully caustic. **Solubility.**—In less than 1 part of water, in about 1.5 parts of alcohol (90 p.c.), and in 2 parts of glycerin. Watery solution is acid to litmus.

PHARMACOLOGY AND THERAPEUTICS OF ZINC CHLORIDE

The chloride is a powerful caustic characterised by its property of burning deeply and not spreading sideways like caustic potash. It is also painless. Therefore it has been used to destroy exposed tooth pulp in carious teeth, wart, condyloma and lupus. In dilute solutions (1 in 10 of water) it forms a good stimulating application for ulcers failing to heal from want of vitality. It may also be used as a disinfectant for washing out cavities and wounds with putrid discharge. A weak solution (1 to 2 grs. to 1 pint) forms a useful injection for gonorrhœa.

It is the principal ingredient of Burnett's Disinfecting Fluid, a well-known household disinfectant for cleaning utensils in the sick room of fever patients; it quickly permeates or disintegrates all organic matter with which it comes in contact. The chief objection to its use is that it is highly poisonous, and being devoid of any smell or colour it may be taken accidentally. The chloride is highly corrosive and poisonous and should never be given internally.

ZINCI SULP AS

Zinc Sulphate. (Zinc. Sulph.). $\text{ZnSO}_4, 7\text{H}_2\text{O}$

Syn.—White Vitriol.

Source.—By the interaction of zinc and sulphuric acid. Contains not less than 99.5 p.c. and not more than the equivalent of 101 p.c. of zinc sulphate.

Characters.—Colourless, transparent crystals, with a strong metallic styptic taste. Odourless. **Soluble** in less than 1 part of water.

Incompatibles.—Alkalies and their carbonates, lime-water, lead acetate, silver nitrate, vegetable infusions, and milk.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.; 10 to 30 grs. or 0.6 to 2 grm. as emetic.

OFFICIAL PREPARATION

1. Unguentum Zinci Oleatis —Zinc Oleate 50 p.c.

ZINCI STEA AS

Zinc Stearate. (Zinc. Stear.)

Source.—Prepared by the interaction of a soluble zinc salt and a solution of sodium salt of stearic acid of commerce. Consists chiefly of zinc stearate with variable proportions of zinc palmitate. Contains not less than 13 p.c. and not more than 15.5 p.c. of zinc oxide.

Characters.—A light, white, impalpable amorphous powder, free from grittiness; odour, characteristic. *Insoluble* in water, in alcohol (90 p.c.), and in ether.

NON-OFFICIAL PREPARATIONS

1. **Zinci Carbonas.**—A white, tasteless, inodorous insoluble powder
2. **Calamina** *Syn*—*Prepared Calamine.*—Prepared by calcining native carbonate of zinc and reducing it to an impalpable powder and suitably coloured with iron oxide. A pale, pinkish powder, without grittiness
3. **Lotio Calaminæ**—Prepared calamine 3 oz, zinc oxide 1 oz., glycerin 1 oz, rose water to 20 oz. In *eczema*, and to conceal acne spots on the face.
4. **Zinci Phenolsulphonas** *Syn*—*Zinc Sulphocarbolate*—Colourless, transparent, efflorescent crystals. Soluble, 1 in 2 of water. As an injection in *gonorrhœa* (2 to 3 grs. to 1 oz.)

ZINCI OXIDUM

(Zinc, Oxid)

Zinc Oxide. ZnO

Syn.—Chinese White.

Source.—Obtained from metallic zinc by combustion in air. Contains not less than 99 p.c. of zinc oxide.

Characters.—A soft, white or nearly white, tasteless and amorphous powder, becoming pale-yellow when heated. Insoluble in water. Soluble in solutions of sodium hydroxide and dilute mineral acids.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATIONS

1. **Unguentum Zinci Oxidi.** *Syn.*—*Zinc Ointment.*—15 p.c.
2. **Pasta Zinci Oxidi Composita.** *Syn.*—*Zinc Paste, Lassar's paste.*—Zinc oxide 25 p.c.
3. **Gelatinum Zinci.** *Syn.*—*Unna's Paste.*—Zinc oxide 15 p.c.

PHARMACOLOGY OF SULPHATE, OXIDE AND STEARATE OF ZINC

Externally.—The insoluble salts like the oxide, the carbonate and the stearate are mild antiseptic and astringents, and are used as local sedatives. Their action resembles lead and silver salts, *i.e.* they precipitate the proteins in the discharges and in the tissues

Internally.—The sulphate has a metallic taste and acts as an emetic like copper but less irritating, though quite effective and prompt, and not followed by any depression. In large doses it is a powerful gastro-intestinal irritant causing vomiting, purging, abdominal pain and collapse. The oxide and the carbonate are less irritant to the stomach, but their prolonged use causes dyspepsia and constipation, and occasionally diarrhœa.

Zinc is eliminated by the stool, and in smaller amount by the bile and the urine. It is absorbed and stored up in the liver and to a less extent in the spleen, the kidneys, and the thyroid.

Little is known of its systemic effect. After prolonged

use the symptoms closely resemble plumbism. In zinc mines of Silesia the workers suffer from obstinate catarrh of the respiratory tract, catarrh of the throat and constriction of the chest, a metallic taste in the mouth, gastro-intestinal irritation, general cachexia, cramps, lassitude and joint pains. Intermittent attacks of fever, known as *brass founder's ague*, sometimes occur from constant inhalation of the fumes. Some obscure nervous symptoms have been attributed to it. It depresses the central nervous system, the heart, and the muscles.

THERAPEUTICS OF SULPHATE, OXIDE AND STEARATE OF ZINC

Externally.—The sulphate (2 grs. to 1 oz. of water) forms an excellent and stimulating application for wounds and ulcers, and as an astringent injection in gonorrhœa, leucorrhœa, otitis, etc. It is used as an eye lotion in conjunctivitis* provided there is no ulceration of the cornea.

As a mild astringent and sedative the oxide is used as a dusting powder mixed with talc powder or as an ointment or paste in various skin affections of children. As it lessens secretion it is used as a drying application in eczema and intertrigo†.

Internally.—The sulphate is used internally as an emetic in cases of poisoning. The oxide has been used in hysteria and epilepsy, and with belladonna to check the night sweats of phthisis; possibly it is of little value in these cases.

CUP I SULP AS

(Cupr Sulph.)

Copper Sulphate. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

Syn.—Blue Vitriol: Blue Stone. Syn. I V.—*Tutia*. Beng., Hind.

Source.—Obtained by the action of sulphuric acid on copper. Contains not less than 98.5 p.c., and not more than the equivalent of 101 p.c. of Copper Sulphate.

Characters.—In blue triclinic prisms, or a blue crystalline powder. Solubility.—1 in 3 of cold water, almost insoluble in alcohol (90 p.c.).

Incompatibles.—Alkalies and their carbonates, lime water, mineral salts (except sulphates), iodides, and many vegetable astringents.

B.P. Dose.— $\frac{1}{4}$ to 2 grs. or 0.016 to 0.12 grm.; 5 to 10 grs. or 0.3 to 0.6 grm. as an emetic.

NON-OFFICIAL PREPARATIONS

1. *Lapis Divinus*. Syn.—*Cuprum Aluminatum*—Powdered copper sulphate, potassium nitrate and alum, of each equal parts melted in a porcelain dish, add camphor 1 and alum 1, fuse. 2 grs in 1 oz. of distilled water makes a good eye-wash

2. *Unguentum Cupri Oleatis*, B.P.C.—Copper oleate 12.5; yellow soft paraffin 87.5, melt and mix. An excellent antiseptic and parasiticide. Useful in ringworm, hard and horny warts and corns.

*R

Zinc. sulph grs 4
Acid boric grs. 10
Aq. dest. ad oz 1

†R

Calamin. gr. 120
Zinc Oxid. gr 120
Ol. Oliv. oz. 1
Aq. Calcis oz. 1

PHARMACOLOGY

Externally.—Copper sulphate has no action on the unbroken skin, but is a caustic when applied to a raw surface or a delicate mucous membrane, such as that of the conjunctiva. In dilute solutions it constricts local blood-vessels and it is therefore a local astringent. It is an antiseptic and in dilutions of 1 in 1,000,000 of distilled water, 1 in 50,000 of tap water, and 1 in 1,000 of sea water kills *B. typhosus* in two hours. The presence of organic matter still further reduces this action. It is highly poisonous to algæ, fungi and protozoa. It is however not a reliable bactericide, though fairly efficacious for the bacilli of the colon group.

Internally. Gastro-intestinal tract.—In small doses copper has a harsh metallic taste, and acts as an astringent, and in large doses (5 to 10 grs), as an emetic like zinc sulphate. Emesis is caused by its action on the stomach, when it is expelled out and no further effect is observed. If it fails to induce vomiting the stomach must be quickly emptied, otherwise gastro-enteritis may result with symptoms of acute corrosive poisoning, causing abdominal pain, vomiting, tenesmus and violent diarrhœa. As a rule large single doses do not cause any harm as they are rapidly removed by vomiting.

Absorption and elimination.—Copper is absorbed with difficulty in minute quantities, either when given by the mouth or from wounds and other mucous surfaces, and is stored up in the liver, spleen and kidneys. It is eliminated almost entirely by the fæces, also by the bile, urine, saliva and sweat.

Copper in minute quantities is present in the mammalian tissue, and is supposed to aid iron in the formation of hæmoglobin in young animals (Hart and Steenbock). It has been shown that a combination of copper and iron improves induced anæmia more quickly than when iron is administered alone. It does not help absorption or storage of iron and does not enter into the formation of hæmoglobin, but is said to act as a catalytic agent in its formation. It is normally present in the food, specially vegetable food, and enters into a firm compound with chlorophyll.

Acute toxic action.—This is rare. In large doses copper salts produce violent gastro-intestinal irritation, causing vomiting sometimes of bluish colour, metallic taste in the mouth, abdominal pain and symptoms of gastro-enteritis. Death may occur from cardiac and respiratory failure.

Antidotes—Emetics or stomach pump if there is no free vomiting; white of egg, milk or demulcent drinks; yellow prussiate of potassium, followed by opium and a warm poultice over the stomach.

Chronic toxic action.—Workers in copper or brass may suffer from anæmia, headache, debility, emaciation, indigestion tremors, laryngeal and pharyngeal catarrh, occasional hæmoptysis, salivation, a green line at the bases of the teeth and occasional colic, in short a condition not unlike that of lead poisoning.

THERAPEUTICS

Externally.—Copper sulphate in the form of sticks is used to destroy exuberant granulations, and as a lotion (2 to 4 grs. to 1 oz.) to stimulate indolent ulcers. Being not so strong as silver nitrate, it causes less pain when applied to granular lids and to the edges of the eyelids in tinea tarsi. It is largely used in the form of *lapis divinus*. Ung. cupræ oleatis is an excellent remedy for ringworm.

It has also been used to sterilise water infected with typhoid bacillus, but the proportion of copper is greater than required to kill algæ. In strengths of 1 in 2 to 10 millions it removes algæ and other vegetable growths from the water.

Internally.—Very rarely used internally, but has been recommended in $\frac{1}{4}$ to 1 gr doses in actinomycosis and sporotrichosis. For its emetic action, it is occasionally used in narcotic poisoning in 1 p.c. solution. It is a valuable antidote in poisoning by phosphorus; here it acts not only as an emetic, but forms insoluble copper phosphide which is not absorbed. 3 grs. of copper sulphate should be given every few minutes until vomiting is induced and then a saline laxative.

ALUM N

Alum. (Alum.)

Syn.—Alumen Purificatum.

Syn. I.V.—*Fatkiri*, Beng. *Futkiri*, Hind.

Sources.—Obtained by the combination of aluminium sulphate with potassium sulphate, and contains not less than 99.5 p.c. of potash alum; or by the combination of aluminium sulphate with ammonium sulphate, and contains not less than 99.5 p.c. of ammonia alum.

Characters.—Colourless, transparent, crystalline masses, or a white powder; taste, sweetish and astringent. Melts when heated and loses water of crystallisation and forms anhydrous salt. Very soluble in water; insoluble in alcohol (90 p.c.); freely soluble in glycerin.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATION

1. Glycerinum Aluminis.—13 p.c. potash alum. B.P. Dose.—30 to 60 ms. or 3 to 4 mils.

NON-OFFICIAL PREPARATIONS AND ALLIED DERIVATIVES

1. Collyrium Aluminis, B.P.C.—Alum, 10 G., distilled water to 1000 mils
2. Gargarisma Aluminis, B.P.C. Syn.—*Alum Gargle*—Glycerin of alum, 125 mils, acid infusion of roses q.s 1000 mils
3. Aluminii Aceto-Tartras Syn.—*Asol.*—In shining masses, soluble in water. Astringent and antiseptic 1 or 2 p.c. solution as gargle, lotion or douche
4. Aluminii Hydroxidum.—Prepared by precipitating solution of alum with sodium carbonate White, bulky, amorphous powder. Odourless and tasteless. Insoluble in water. Dose—5 to 10 grs or 0.3 to 0.6 grms. Colloidal aluminium hydroxide tablets are sold under the name of *Alocol* Useful in *fatulence, hyperacidity, peptic ulcer*, etc

PHARMACOLOGY

Externally.—Alum has no action on the unbroken skin, but coagulates the albumin of discharges and tissues. It

therefore forms a covering on ulcers and sores, and arrests bleeding. Hence, it is a valuable local astringent and hæmostatic. Dried alum is a mild caustic because it abstracts water.

Internally.—Alum is a local astringent to the mouth and throat, imparting an astringent taste, and a feeling of dryness to the throat. In small doses (3 to 4 grs.) it has the same astringent action on the stomach and intestine as on the raw skin, producing constipation. Its hæmostatic action is entirely local. In 30 to 60 grs doses it causes vomiting by directly stimulating the peripheral nerves of the stomach, and in still larger doses it is a gastro-intestinal irritant causing vomiting and purging. Very little is absorbed, so that no symptoms of poisoning are elicited even after prolonged use. The small amount absorbed is stored in the liver, kidney, etc., and slowly eliminated in the bile and urine. When injected per rectum, it kills thread worms.

Elimination.—Alum is probably absorbed into the blood as an albuminate, and has no remote action on the tissues in medicinal doses. It is chiefly eliminated with the fæces and partly by the skin, bile and kidneys.

THERAPEUTICS

Externally. Skin.—In the form of powder or in a concentrated solution, it stops bleeding from leech bites, wounds, and superficial cuts. A weak solution of alum and borax (1 p.c. of each) checks the discharge of weeping eczema.

Nose.—Its solution makes a useful collunarium in ozæna. Powdered alum either sniffed up or blown in by means of a paper funnel, or its lotion (10 grs. in 1 oz.) injected into the nostrils, arrests epistaxis.

Eyes—Alum makes a useful collyrium (4 to 8 grs. in 1 oz.) for ordinary or purulent conjunctivitis.

Genitals—It makes a capital wash (60 grs. in 1 pint) for vulvitis of children, if the parts are frequently irrigated and a piece of lint soaked in the lotion is left *in situ*. It also relieves pruritus. A douche (10 grs. to 1 oz.) removes leucorrhœa, checks slight hæmorrhage from patulous os after abortion or delivery. A weak solution (3 grs. in 1 oz.) is successfully employed in gonorrhœa as an injection.

Internally. Mouth.—Alum is commonly used as a dentifrice in ulcerated and spongy gums. A solution (5 to 10 grs. in 1 oz.) is a useful gargle in sore throat, elongated uvula, tonsillitis, salivation, and aphthous and ulcerative stomatitis, but Glycerinum Aluminis is a better application in these cases. In the form of a spray, alum may be employed in hoarseness and chronic coughs.

Stomach and intestine.—As an astringent, alum is used in chronic diarrhœa and as a local hæmostatic in gastro-

intestinal hæmorrhage. Alum-whey obtained by curdling 1 pint of milk with 120 grs. of alum may be given with benefit in enteric and other diarrhœas. In 30 gr. doses frequently repeated, it is of special value in lead poisoning and relieves colic by precipitating lead salts as insoluble lead sulphates.

KAOLINUM

Kaolin. (Kaolin.)

Source.—A native aluminium silicate, powdered and freed from gritty particles by elutriation.

Characters.—A soft whitish powder, insoluble in water, and in mineral acids.

B.P. Dose.— $\frac{1}{2}$ to 2 oz. or 15 to 60 grm.

OFFICIAL PREPARATION

1. *Cataplasma Kaolini.* *Syn.*—*Kaolin Poultice.*—Should be kept in well closed containers.

NON-OFFICIAL PREPARATIONS

1 *Unguentum Kaolini*, B.P.C. *Syn.*—*Kaolin Mass.*—White soft paraffin 50, hard paraffin 25, melt, and add kaolin 25, stir until cold. An emollient application to abraded surfaces, and a useful excipient for silver nitrate, potassium permanganate, and bichromate pills.

2 *Emulsio Paraffini Liquidi et Kaolini*, B.P.C.—Liquid paraffin, 5 oz., powdered acacia, 300 grs., tragacanth powder, 87½ grs., kaolin 3¾ oz., chloroform water q.s. 20 oz. *Dose.*— $\frac{1}{2}$ to 2 oz. or 15 to 60 mls.

USES

Besides its use as an excipient in the preparation of pill masses, specially for substances which contain oxidising agents, kaolin can be employed as a dusting powder in intertrigo, weeping eczema, etc. The cataplasma forms a valuable poultice in relieving deep-seated inflammation, and may be applied hot on a piece of thick cloth or lint in pleurisy, pneumonia, pericarditis, inflamed joints, hepatitis, etc., where it gives much relief. It should be changed every twelve to twenty-four hours, and kept in place with a bandage.

Internally—Kaolin has two important actions, *viz.*—(1) forms a coating on the intestinal wall thus protects it from irritating particles and digestive juices and reduces peristalsis; (2) adsorbs poisons and bacterial toxins. For its former effect it is used in diarrhœa and ulcerative colitis, while for the latter in cholera, dysentery, etc. The usual practice is to mix 100 grm. in 250 c.c. of water, half a pint of this is given every half hour for the first twelve hours, and several glasses are taken during the next twelve hours. Being a very efficient adsorbent, colloidal kaolin (*Osmo Kaolin*) is extensively used for adsorption of bacteria and toxins from the intestine thus preventing their absorption. *Kaolin has no direct disinfecting action on the intestine.*

ALTERNATIVE

Gold

AU I ET SODII C LO IDUM(*Not official*)

Source and Characters—A mixture of equal parts of anhydrous gold chloride and anhydrous sodium chloride. Orange-yellow powder. Odourless. Taste, saline, metallic. Very soluble in water. Yields 50 p.c. gold.

Dose— $\frac{1}{30}$ to $\frac{1}{12}$ gr. or 0.002 to 0.005 gm.

NON-OFFICIAL PREPARATION

1 **Liquor Auri et Arseni Brominatus, B.P.C.**—Contains $\frac{1}{24}$ gr. arsenious anhydride and $\frac{1}{12}$ gr. gold tribromide in 10 ms. **Dose**—5 to 10 ms. or 0.3 to 0.6 mil.

AURI ET SODII THIOSULP AS(*Not official*)

Syn—Sanocrysin, Chisalbin.

Characters.—A double thiosulphate of gold and sodium. Solid, snow-white substance in long needle-like crystals freely soluble in water. Solution neutral.

Dose— $\frac{2}{5}$ to 15 grs. or 0.025 to 1 gm. in 10 c.c. of distilled water at intervals of 3 to 4 days intravenously.

SO IUM AU OT I ALATE(*Not official*)

Syn.—Myocrisin.

A preparation containing 50 p.c. gold.

Dose—0.01 gm. initial dose, increased gradually to 0.05, 0.1 and 0.2 gm. in 8 to 10 injections.

N.B.—An interval of 4 to 6 weeks should be allowed after one course.

ACTION AND USES

Gold in different forms has been used empirically in diverse conditions. It is much less poisonous than other heavy metals, although its salts when given in toxic doses produce vomiting and purging. Given intravenously it acts like arsenic, and produces a fall of blood pressure by dilating the mesenteric vessels. It is said to help absorption of pathological connective tissues. In combination with arsenic it has been used in tertiary syphilis, and with bromides in epilepsy. It is used in neurasthenia, but any benefit that may follow its use is possibly mental.

The chief interest of gold at the present time centres on its supposed value in tuberculosis and Moellgaard introduced it in the form of sanocrysin. How it acts is not clearly understood and it has been suggested that it penetrates the lipid covering of the bacilli which it kills. It is also possible that it stimulates phagocytosis of the reticulo-endothelial tissues. It has no marked effect on tubercle bacilli *in vitro*, and Moellgaard claimed that it has a direct bactericidal effect in the animal body, but this view has been discarded. It has been suggested that it acts as a catalytic agent and brings about the acceleration of slow spontaneous healing processes by stimulating the activity of the reticulo-endothelial system. The injections are often followed by some reaction, such as albuminuria, fever, exanthemata, loss of weight and intestinal disturbances. There may also be some focal reaction. These symptoms are likely to occur when an injection is given while the patient still shows a febrile

reaction from the previous injection or when the patient is febrile before the first injection is given. They are probably due to an overdosage. Knud Secher believes that the reactions are due to liberation of toxins. He therefore bases his initial dosage on the assumption that in "open cases" the toxins can be excreted by the air passages and therefore larger doses are permissible, while in "closed cases" smaller doses are indicated because the toxins having no outlet, pass into the blood stream. An intravenous injection of antitoxic serum prevents the appearance of these symptoms and makes the treatment with sanocrysin more safe. This serum is prepared by injecting calves with tubercle bacillus killed by heat, and with tuberculin. The serum of horses injected with diaplyte (defatted tubercle vaccine) gives better results.

Although it is too early to properly assess its value as a remedy for pulmonary tuberculosis, the reports of the Medical Research Council are favourable. Under its use the tubercle bacillus disappears in early cases and there is diminution of sputum, cough and pyrexia. The first report records 2 deaths directly caused by sanocrysin out of 30 cases. Early cases certainly improve but the results are not so favourable in advanced cases. The regulation of the dose is an important factor and if not carefully done will make the condition worse.

Like other heavy metals sanocrysin produces cumulative effects when given in large doses, or at frequent intervals.

In the form of myocrysin gold is extensively used in the Continent in rheumatoid arthritis. It is given intramuscularly, commencing with doses of 0.01 grm. and then slowly working up to 0.2 grm. in 8 to 10 injections, and a total of 2 grm. forms a course. An interval of 4 to 6 weeks is given before starting another course. Generally two to three courses are required.

Combined ionisation and gold treatment has given very favourable results in lupus, and its action has been explained as an indirect one, of the nature of a regressive influence on the pathological tissue and upon the altered blood vessels. In lupus erythematosus, sanocrysin has been used with good results. The initial dose is 0.001 grm. gradually increased to 0.05 grm. It is given once a week intravenously.

Excretion.—About 50 p.c. of the metal is eliminated by the kidneys and partly by the intestine. Part is retained in the liver and muscle for a long time.

Ordinary symptoms of overdosage are: fever, malaise, albuminuria, stomatitis, vomiting, diarrhoea, erythema, exfoliative dermatitis and focal reactions in the disease under treatment. Sometimes nervous complications are observed. They are: mental agitation; depression; apprehension and fear of some unknown calamity; insomnia; excessive flushing and sweating; fatigue; twitchings of muscles of trunk and limb and a choking feeling in the throat.* Sodium thiosulphate relieves these symptoms.

Mode of administration.—The usual dose of sanocrysin for Indian patients is smaller, and the initial course should be as follows:—0.05, 0.1, 0.2, 0.3, 0.5, 0.65, 0.75 and 1.0 grm. The maximum dose is seldom required. The optimum dose should be repeated till a total of 4 to 5 grm. has been given. In weak and febrile patients it is better to begin with 0.025 grm. ($\frac{1}{4}$ gr.). The usual method of administration is the intravenous route, once a week, and a 5 p.c. solution being almost isotonic with blood should be used. For intramuscular injection a 3 p.c. solution in sterile water, or a 5 p.c. oily suspension is preferable, as this is less liable to cause local irritation. Oily preparations are better and safer since they can be administered intramuscularly, and the toxic effects and other reactions are much less. Moreover

*H Hughes Jones, *British Medical Journal*, Jan 9, 1937

the absorption being slow the effects are prolonged. An all-glass syringe with a platinum needle should be used as the drug acts on steel. The injection should be given in the morning by choice and the patient kept in bed during the course of treatment. Examine the urine daily for albumin and cast and make a note of the temperature for any febrile reaction. It should never be given subcutaneously.

Indications for the use of sanocrysin have been summarised by G. Gregory Kayne as follows—*

(1) *Recent lesions* (i.e. those associated with symptoms of not more than three to four months' duration) *of the exudative type* (showing fluffy-edged soft X-ray shadows) When cavitation is present it may be used, but artificial pneumothorax should be done.

(2) *Recent exudative lesion occurring in association with old standing disease.*

(3) In patients in whom suggestive shadows are found in routine examinations in the absence of definite clinical evidence of activity.

Solganal.—Di-sodium salt of 4-sulphomethylamino-2-auronercaprobenzol-1-sulphonic acid. Contains 36·5 p.c. of gold. In *tuberculosis*. *Dose.*—0·005 to 0·5 grm. *intravenously* to be given once or twice a week according to reaction. The dose to be cautiously increased.

Solganal-B is solution, and **Solganal B Oleosum** is oily suspension, of aurothioglucose, for *intramuscular and subcutaneous use*. The initial dose for Indian patients should not be more than one-fourth of the minimum dose recommended, and if this is not followed by any febrile reaction then the dose may be increased by the same amount with each subsequent injection. Unless the dose is carefully regulated it may cause severe reaction and make the condition worse. *Dose.*—0·005 to 0·5 grm

DEPILATORY

Thallium

THALLII ACETAS—Prepared by neutralising an aqueous solution of Thallous Hydroxide with acetic acid. In colourless needles, or in white crystalline powder, soluble in water

Dose.—0·008 grm. per kilogram of body weight (oi $\frac{2}{32}$ gr. per pound)

ACTION AND USES

Thallium salts produce no immediate effects on animals beyond causing some relaxation of the plain muscles, but a few days later (generally a fortnight) cause shedding of the hair in all animals. Its chief use is as a depilatory in cases of ringworm of the scalp, when the hair becomes brittle in a week's time and falls off within the next week, and the hair starts to grow in about the same time. It is generally administered in tablets or sweetened aqueous solution, and since children tolerate it better its use is confined to children under ten years of age. As a rule one dose is sufficient and the drug is not repeated within a period of three months.

Since the drug is apt to produce toxic symptoms it should be used with extreme caution, and the dose should be well regulated. Large doses will cause shedding of hair from all parts of the body innervated by the sympathetic. Toxic symptoms are vomiting, diarrhoea, stomatitis, albuminuria, joint pains confined to lower limbs, peripheral neuritis, delirium and collapse. Remember that the *margin of safety* between the epilation dose and the toxic dose is very low, and it should not be used when there is albuminuria or any general constitutional disease.

Treatment of poisoning.—Stomach wash or an emetic followed by a purgative. In acute cases dextrose intravenously. Caffeine or adrenaline to overcome shock, and sodium iodide (5 to 15 grs. daily)

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to convert the toxic soluble thallium salts into almost insoluble iodides. Sodium thiosulphate (5 to 15 grs. daily) intravenously to promote gradual elimination. Children should receive proportionately smaller doses.

GROUP IV: METALLOIDS

Bismuth, Arsenic, Antimony, Chromium, Phosphorus

Bismuth, Arsenic and Antimony will be discussed with other Chemotherapeutic Agents

CHROMIUM TRIOXIDE

Chromium Trioxide. (Chrom. Triox.)

Syn—Acidum Chromicum, Chromic Anhydride

Source—Obtained by the interaction of sulphuric acid and potassium dichromate. Contains not less than 95 p.c. CrO_3

Characters.—Dark-red, acicular crystals, or dark-brown masses. No odour, deliquescent and corrosive. *Freely soluble* in water and in ether

N.B.—Liable to cause combustion or explosion when in contact with alcohol, ether, glycerin and other organic substances

PHARMACOLOGY

Externally.—It is a powerful oxidising agent, destroying the lower organisms, and is therefore a deodorant and disinfectant. It is powerfully hygroscopic and takes up water from moist tissues and oxidises organic substances, and acts as a caustic.

THERAPEUTICS

Externally.—Liquor acidi chromici (25 p.c. solution) is used for destroying warts. It should be applied with a pointed glass rod, the adjacent parts being protected by a plaster or ointment, and a piece of wet lint kept ready to absorb any superfluous acid. A weak lotion (1 in 40 or more) is useful for ulcerated gums and foul sores. A 3 per cent. solution checks perspiration of the feet.

Chromic acid solution does not burn or stain linen, and is a delicate test for albumin in the urine.

PHOSPHORUS

Phosphorus. (Not Official)

Source—A solid non-metallic element, obtained from calcium phosphate

Characters—A semi-transparent, wax-like solid, emitting white vapours and is luminous in the dark, ignites in the air. **Solubility**—Insoluble in water; soluble 1 in 25 of chloroform, 1 in 350 of alcohol (90 p.c.), 1 in 80 of olive oil and of ether; 2 in 1 of carbon disulphide, 1 in 60 of oil of turpentine.

Dose— $\frac{1}{100}$ to $\frac{1}{25}$ gr. or 0.0006 to 0.0025 grm

NON-OFFICIAL PREPARATIONS

1. **Pilula Phosphori**, B.P.C.—Each pill contains $\frac{1}{100}$ gr. of phosphorus
Dose.—1 to 4 pills

2. **Liquor Phosphori Co**, B.P.C. **Syn**—*Tinct. Phosphori Co*.—Phosphorus 2 grm, chloroform 175 mil., dehydrated alcohol to 1000 mil. **Dose**.—3 to 12 ms. or 0.2 to 0.8 mil.

3. **Calci Hypophosphis**.—A white, crystalline pearly salt. Taste, bitter, nauseous. Soluble 1 in 8 of water. **Dose**.—3 to 10 grs. or 0.2 to 0.6 G.

4. **Syrupus Calci Hypophosphitis**, B.P.C.—Contains 1 gr. per 1 dr. **Dose**—1 to 4 drs. or 4 to 16 mils

5. **Calcii Glycerophosphas**.—A calcium salt of glycerophosphoric acid. A fine, white, hygroscopic odourless powder. **Dose**—3 to 10 grs. or 0.2 to 0.6 G.

6 **Ferri Glycerophosphas.**—*Dose* —1 to 5 grs. or 0.06 to 0.3 G.

7. **Sodii Glycerophosphas.**—*Dose* —5 to 10 grs or 0.3 to 0.6 G.

8 **Syrupus Glycerophosphatum Compositus, B.P.C.**—Contains $\frac{1}{100}$ gr of strychnine, $\frac{1}{4}$ gr cal. glycerophosph, about $\frac{1}{2}$ gr. each of potassium, sodium and mag glycerophosph, and about $\frac{1}{2}$ gr each of non glycerophosph and caffeine in 1 dl. *Dose.*—1 to 2 dis or 4 to 8 mls

PHARMACOLOGY

Phosphorus is an important constituent of the body and forms about 0.7 p.c. of the body weight. It exists in the bone as phosphate of calcium and magnesium, and as soluble phosphate ions in the blood and other fluids, and as nuclein, lecithin and phosphatides in the tissues and plasma. As a therapeutic agent its value is limited, although it has a specially interesting physiological action. As a poison it is important.

Stomach and liver.—In moderate doses it causes nausea and vomiting. The epithelial cells of the stomach and intestine undergo fatty changes giving rise to abdominal pain, vomiting and diarrhoea; the vomited matter having a garlic odour. These symptoms *do not appear immediately after administration, but are delayed for hours and days.* The liver is affected early causing fatty changes, and becomes enlarged, painful and tender. Jaundice is a marked symptom and is due to the cells being infiltrated with fat which press on the bile capillaries and occlude them.

Blood.—Phosphorus is absorbed in the small intestine and circulates as such. In therapeutic doses it increases the number of red blood corpuscles, although it was formerly believed to have a destructive action on the red blood cells. It has however no such action even in severe poisoning. It retards coagulation of the blood due to destruction of fibrinogen or fibrin ferment, or to the formation of peptone bodies from protein destruction. This factor and the fatty degeneration of the endothelial tissue of the capillaries account for hæmorrhage in poisoning.

Bones.—When continued long in such minute doses as not to affect the stomach or liver, it has a specific action on the bone. There is an increased osseous deposit and the long bones become more dense at the expense of the cancellous tissue. Instead of the porous bone tissue filled with red marrow there develops from the epiphysis line a dense, hard substance of the same nature as that forms on the outer shell on the diaphysis. Phosphorus therefore stimulates growth of bones, *i.e.* there is an excess of anabolic over the katabolic processes in the metabolism of bony tissue. The bone-marrow in chronic poisoning becomes hyperæmic, the fat cells disappear and the leucoblastic cells increase.

Metabolism.—In small doses continued long phosphorus stimulates metabolic processes and helps growth and formation of new tissue. The destructive effects are observed in chronic poisoning, or as a secondary process after a single large dose. The main symptoms are characterised by increased tissue destruction with disturbances of synthesis, oxidation and dissociation. Less fat but more carbohydrate and protein are broken up, though imperfectly, and the excretion of nitrogenous metabolites, *viz.* amino acids, leucin, tyrosin and peptone like bodies is increased. The excretion of urea is not increased, on the contrary may be diminished, but there is an excess of ammonia which enters the blood to neutralise acidosis formed by the production of lactic acid and other organic acids as a result of incomplete oxidation of fat, glycogen, etc. The respiratory interchange is diminished and oxygen consumption and carbonic acid excretion is reduced. The cause of this diminished oxygen intake is not definitely settled, although it has been suggested that phosphorus renders the cells less capable of utilising oxygen.

Fatty infiltration occurs in almost all organs of the body, that of

the liver being most extensive. Another important effect is the change in the carbohydrate metabolism with disappearance of glycogen from the liver. The increased excretion of nitrogen has been regarded as the result of this effect since the body draws on the protein to make up the deficiency of the carbohydrate. Moreover, the emptiness of glycogen of the liver leads to mobilisation of the fats to supply the want, and since the liver cannot utilise the fat completely it is deposited in the cells of this organ.

Absorption and elimination.—Absorption is slow and occurs from the intestine, and to some extent by the lungs when inhaled. The systemic effects are therefore delayed several days. As it is soluble in oily substances, presence of oil and fats in the intestine favours absorption. A portion is oxidised to phosphoric acid and some phosphorus is excreted by the lungs and urine.

Acute toxic action.—Acute poisoning may occur from swallowing rat-paste or lucifer match-heads. Besides gastro-enteritis already described, there is considerable prostration and occasionally collapse and death. Generally these symptoms come on in a mild form, and the patient does well for a few days. Then, after an interval, jaundice is noticed, with a tender, enlarged liver. The jaundice soon deepens, vomiting, which may be luminous, and purging of dark-coloured blood set in, temperature first rises and then falls, the pulse becomes weak and rapid, the skin cold and clammy, and the urine scanty, high-coloured and albuminous. Muscular twitchings, convulsions or coma supervene, terminating in death. Abortion frequently follows possibly due to degeneration of the blood vessels. Fatty degeneration of the liver, with general ecchymosis and hæmorrhages are the common P.M. appearances.

Antidotes.—Stomach-pump, or emetics, copper sulphate is the appropriate emetic. It should be given in 3 gr. doses every 10 minutes till vomiting takes place, and then 1 gr. every quarter of an hour as an antidote as it oxidises the phosphorus and envelops the globules with a coating of reduced copper or forms copper phosphide which retards absorption. The stomach should be washed out with a 0.2 p.c. solution of potassium permanganate which converts phosphorus into phosphoric acid. Ozonized oil of turpentine was used formerly but has been found to be of no value. Alkalies may be given afterwards to neutralise acidosis, and demulcent drinks. Avoid fats, butter and oils which dissolve phosphorus.

Chronic toxic action.—Chronic poisoning is rare, and occurs only in those workmen who are exposed to the fumes of phosphorus. Gastro-enteritis, fatty degeneration, necrosis of the jaw, general tuberculosis are the prominent symptoms. Phosphorus fumes attack the bone through carious teeth or spongy gums, but this effect is not produced by its internal use.

THERAPEUTICS

As a nervine tonic, the hypophosphites and the glycerophosphates have been given in nervous exhaustion, over-taxation of the brain from prolonged strain and overwork, but as they pass unchanged through the system and can be almost entirely recovered from the urine, they can furnish no phosphorus to the nerve tissue. They are used largely in wasting diseases like phthisis, and in chronic bronchitis, but with doubtful results. Phosphorus has been given in affections dependent on malnutrition, such as anæmia, leucocythæmia, with occasional success. Dr. Kussowitz, obtained very good results in the rickets of children, the dose being $\frac{1}{10}$ to $\frac{1}{8}$ gr. *per diem* for a child weighing 12 lbs. It is no doubt useful in ununited fractures, specially during pregnancy, and in osteomalacia. But the use of phosphorus in these conditions has been given up in favour of cod-liver oil, vitamin D, ultra-violet rays, and sunlight.

GROUP V

DRUGS ACTING ON THE NERVOUS SYSTEM

By the nervous system we mean the brain, the bulb, the cord, the nerves, both sensory and motor, and the various ganglia. The highest motor and sensory centres as well as those of volition, intellect, emotion, etc., are contained in the cerebral convolutions, while the simple automatic and reflex centres are in the basal ganglia, cerebellum, medulla and cord. All nerve centres are connected with one another by nerve filaments called *collaterals*, for co-ordination of impulses. The cerebral or highest centres are not only excitable or capable of being brought into action by afferent impulses, but also possess an inherent power of spontaneously originating impulses themselves. Their action is therefore both *reflective* and *spontaneous*. To the pharmacologist this reflective or *reflex action* is important. It is effected by (1) an afferent sensory nerve ; (2) reflex centre ; and (3) an efferent motor or secretory nerve. An impression excited by an irritant on the skin or other structures of the body is conducted through an afferent nerve *via* the posterior root ganglion, to the spinal cord, where it produces certain protoplasmic disturbance, resulting in a force, which either remains there as potential energy, or is conveyed by a different tract—efferent nerve—to perform some specific action either in the muscle, viscera, or the blood vessels. This process is spoken of as reflex action. This sensory stimulus instead of being reflected from the cord may be conveyed by the sensory tracts to the sensory area of the brain, where it will be perceived as an impression either of pain, heat or cold, and so forth, to be felt at the seat of stimulus, and then lead to volitional conveyance of impulse in the form of movement, etc. It will be observed that although the stimulus originates in the skin or other structures, it is perceived as a sensation in the brain. Thus an impression which is peripheral in origin becomes a sensation which is cerebral, and the result may or may not be volitional.

In considering the action of drugs on the nervous system we find that some affect one centre, while others another ; a few influence the lower centres only ; others centres for emotion and intelligence ; and lastly some alter the nervous mechanism of different viscera.

Drugs acting on the nervous system may be classified as follows :—

Class A . Drugs acting on the brain

- 1 Intoxicant Alcohol
- 2 General anæsthetics and narcotics Chloroform, Ether, Ethylene, Nitrous Oxide, Ethyl Chloride, Vinyl Ether, Cyclopropaine

- 3 Hypnotics and narcotics Opium, Cannabis Indica, Bromides, Chloral Hydras, Chlorbutol, Butyl-chloral Hydras, Paraldehyde, Sulphonal, Methylsulphonal, Barbitone, Soluble Barbitone, Carbromalum, Phenobarbitone, Soluble Phenobarbitone, Nembutal, Amytal, Sodium Amytal, Evipan, Sodium Evipan, Urethane, Hyoseine Hydrobromide

Class B. Drugs acting on the cord

- 1 Convulsant Strychnine

Class C Drugs acting on the autonomic system

- 1 Drugs stimulating the parasympathetic endings Pilocarpine, Physostigmine, Acetyl-choline, Muscarine
 2 Drugs depressing the parasympathetic endings Belladonna, Hyoscyamus, Stramonium
 3 Drugs stimulating the sympathetic endings Adrenaline, Ephedrine, Ergotoxine (small doses), Tyramine
 4 Drugs depressing the sympathetic endings Ergotoxine (large doses), Ergotamine, Apocodeine

Class D Drugs acting on the motor nerve-endings and the ganglia

Curare, Nicotine, Gelsemium, Conium, Lobeline

Class E Drugs depressing the sensory nerve-endings

Cocaine, Procaine Hydrochloride, Orthocaine, Benzocaine, Amylocaine Hydrochloride, Percaine, Hydrocyanic Acid, Urea Quinine

Class F Drugs stimulating the sensory nerve-endings

See Counter-irritants

CLASS A: Drugs acting on the Brain

The structure of the brain being more complicated, our knowledge of the pharmacology of this organ is obscure. Although we can influence the functions of the brain more rapidly, yet we cannot localise the action of drugs, nor the exact manner by which they produce the different symptoms. It has, however, been found that they follow certain laws while acting on the brain; they are:—

(a) *The law of dissolution.*—This was first described by Jackson, and consists of the progressive action of a drug on the nerve centres in the reverse order of their development in animal life, *i.e.* those that are the highest and developed last are affected first, and then the next to highest, and so on, until the lowest ones are affected. Thus alcohol paralyzes the highest centres as those of will, intellect, etc., then those of the muscles, as is evidenced by staggering gait, and lastly those of the heart and respiration.

(b) *The law of primary stimulation and subsequent depression.*—This is well illustrated by the action of a drug which in small doses stimulates certain functions, and in large doses depresses them, *e.g.* chloroform.

The different nerve cells react differently to drugs. Thus the functional activity of the brain is influenced by a special group of drugs; of these some like caffeine, atropine, camphor, cocaine, alcohol, chloroform, etc., excite the brain and are called *cerebral stimulants*. In certain instances the excitement is of a disorderly nature accompanied by incoherence and delirium, and the drugs so acting are known as

*deliriant*s, e.g. atropine; while others produce mirthful and comfortable feelings, when they are called *exhilarant*s, e.g. camphor, cannabis indica. Another set of drugs depresses the activity of the brain and these are known under different names according to the nature of their action, viz.—**hypnotics, narcotics, general anæsthetics**. Alcohol, ether and chloroform produce a certain amount of excitement at the beginning, and subsequently according to the quantity used, alcohol produces *intoxication and narcosis*, chloroform and ether produce *loss of consciousness with general anæsthesia*; and opium, cannabis indica, chloral hydrate, etc., act as *hypnotics or narcotics*.

Others again show a selective action on certain parts of the central nervous system. For instance, morphine while stimulating the cardiac vagus centre depresses the respiratory centre; apomorphine acts chiefly on the vomiting centre; caffeine and cocaine stimulate the psychic centre; atropine and camphor the motor centre; and quite a large number of drugs act on the vital medullary centres. Another group of drugs produces very little effect on the brain but influences the activities of the spinal cord or the different nerve-endings.

1. Intoxicant

ALC L E Y ATU

Dehydrated Alcohol. (Alcoh. Dehyd.)

Syn—Absolute Alcohol; Dehydrated Ethanol, U.S.P.

Source.—Obtained by the removal of water from alcohol (95 p.c.), and subsequent distillation. Sp. gr. 0.7936 to 0.7967. Contains not less than 99.4 p.c. v/v or 99 p.c. w/w of C_2H_5O .

ALC OL

(Alcohol)

Alcohol (95 p.c.)

Source.—A mixture of ethyl alcohol and water, obtained by the distillation of fermented saccharine liquids. Contains not more than 95.2 p.c. v/v or 92.7 p.c. w/w, and not less than 94.7 p.c. v/v or 92.0 p.c. w/w of C_2H_5O .

Characters.—A colourless, transparent, mobile and volatile liquid, with a characteristic spirituous odour. Taste, burning. Burns with a blue smokeless flame.

SPI ITUS T YLATUS IN UST IALIS

(Sp. Meth. Indust.)

Industrial Methylated Spirit

Source.—A mixture made by a legally authorised methylator, of 19 volumes alcohol (95 p.c.) with 1 volume of approved wood naphtha, and is of the quality known as '66 O.P. Industrial Methylated Spirits.'

Characters.—Similar to those of alcohol (95 p.c.), but having in addition the odour of wood naphtha.

OFFICIAL DILUTED ALCOHOLS

1. Alcohol (90 p.c.). **Syn**.—*Rectified Spirit*.—Dilute 948 mls of alcohol (95 p.c.) to one litre with distilled water.

2. Alcohol (80 p.c.).—Dilute 842 mls of alcohol (95 p.c.) to one litre with distilled water.

3. Alcohol (70 p.c.).—Dilute 737 mls of alcohol (95 p.c.) to one litre with distilled water.

4. Alcohol (60 p.c.).—Dilute 632 mls of alcohol (95 p.c.) to one litre with distilled water.

5. Alcohol (50 p.c.).—Dilute 526 mls of alcohol (95 p.c.) to one litre with distilled water.

6. Alcohol (45 p.c.).—Dilute 474 mls of alcohol (95 p.c.) to one litre with distilled water.

7. Alcohol (25 p.c.).—Dilute 263 mls of alcohol (95 p.c.) to one litre with distilled water.

8. Alcohol (20 p.c.).—Dilute 210 mls of alcohol (95 p.c.) to one litre with distilled water.

Note.—On mixing alcohol and water contraction of volume and rise of temperature occur.

The following is the list of wines, showing the amount of absolute alcohol by weight :—

Spiritus Frumenti (Whisky) 40 p.c. $\frac{v}{v}$ of alcohol.

Rum, Gin, and strong Liqueurs, about 51 to 59 p.c.

Hocks, Burgundy, about 9 to 13 p.c.

Spiritus Vini Gallici (Brandy) 40 to 50 p.c.

Sherry, Port, Madeira, about 18 to 22 p.c.

Champagne, about 10 to 13 p.c.

Claret, 8 to 12 p.c.

Cider, 6 to 13 p.c.

Ale and Porter, about 3 to 7 p.c.

Beer, 2.5 to 3.5 p.c.

Koumiss and Ginger Beer, about 1 to 3 p.c.

PHARMACOLOGY OF ALCOHOL

Externally.—Alcohol has a great affinity for water, it coagulates protein and irritates and destroys cells. It is therefore a protoplasmic poison. It is an antiseptic, and it has been found that in the preparation of alcoholic liquors the activity of yeast is retarded when the strength of alcohol reaches 10 p.c. and completely stopped when it reaches 15 p.c. When applied to the skin it evaporates quickly producing a sensation of cold which is more marked when used diluted with water. On the other hand if the evaporation is checked, or if it is rubbed in, it abstracts water from the skin and renders the skin drier and harder. When applied in sufficient concentration (60 to 80 p.c.) it dilates the local blood vessels, produces a feeling of warmth, and renders the skin red, thus acting as a local rubefacient and counter-irritant.

Internally.—Undiluted alcohol has the same action on the mouth as on the skin, *viz.* it coagulates the protein and abstracts water, and acts as a local irritant. It stimulates the nerves of taste and causes a reflex flow of saliva, and excites the psychic secretion of gastric juice.

Stomach and intestine.—The action of alcohol on the stomach may be considered from three points of view : (a) its chemical effect on the stomach contents, (b) its effects on the stomach functions, and (c) its effects on the coats of the

stomach. While it is true that undiluted whisky or brandy will precipitate proteins of food and possibly pepsin, and also interfere with the process of digestion, moderate quantities of diluted alcohol (below 20 p.c.) have only a negligible action on the chemical process of digestion. Wines and malt liqueurs, owing to the presence of organic acid and colloidal constituents, if taken in large quantities, have a deleterious effect on digestion. In the same way red wines, owing to the presence of tannin, retard digestive process by precipitating proteins more than white wines.

In weak solutions, *i.e.* below the strength of 10 p.c., alcohol has practically no effect on the stomach wall beyond dilating the vessels and causing a sense of warmth, but in large and repeated doses, or in concentrated solutions, it irritates the mucous membrane, increases the secretion of mucus, and retards the secretion of gastric juice. If this process is continued over long periods, as in chronic alcoholics, gastric follicles atrophy and dyspepsia becomes permanent.

In moderate strengths and taken with food or after food, it tends to promote digestion by direct stimulation of the fundus of the stomach, causing an abundant secretion of gastric juice. If taken with bitters before food it increases the appetite juice, although a small quantity will often produce manifestations of intoxication. Apart from this effect alcohol appears to have a specific action on the secretion after absorption. As regards motor activity alcohol in weak solutions (10 p.c.) has very little effect if any.

A moderate dose of strong alcohol, *e.g.* whisky or brandy, on reaching the stomach, at once reflexly stimulates the heart, raises the blood pressure, quickens the pulse and increases the respiratory movements. Since it causes dilatation of the vessels, specially of the skin, and increases the functional activity of different organs, alcohol is regarded as a general stimulant. But, as will be seen later, these effects are not dependent upon a direct stimulation of the nerve centres, but are purely reflex phenomena and indirect result of inco-ordination. Irritation of the mucous membrane, emotional excitement and increased movement are responsible for the acceleration of the heart.

In the intestine alcohol is so much diluted by the time it passes the pylorus that it exerts very little effect there. After an excessive amount some reaches the duodenum and acts as an irritant. Brandy has a reputation among the lay public as an astringent in diarrhoea. Owing to increased formation of secretin pancreatic secretion is very largely increased whether alcohol is given by the mouth or per rectum.

Liver.—After absorption alcohol passes directly to the liver through the portal circulation, where it affects the hepatic cells producing inflammation. It may disappear in a

few days if no more alcohol is taken, but if long continued, it establishes permanent changes in the liver leading to **cirrhosis or fatty degeneration**, or both. Moderate amounts as a rule are sufficiently diluted by the portal blood, but excessive drinking surcharges the portal blood with alcohol.

Food value of alcohol.—The question whether alcohol is a food has been much discussed, and the chief point is whether it can be regarded as a protein sparer. Proteins contribute to the formation and repair of tissues; carbohydrates and fats are sources of heat and energy. Since alcohol does not contain any nitrogen, it cannot replace protein and therefore has no power to build tissues. Since about 90 p.c. of alcohol taken disappears in the body and is converted into CO_2 and water, alcohol by virtue of the chemical energy thus liberated can replace carbohydrates and fats in the diet, and in this sense is a **non-nitrogenous food**. Moreover it does not require more energy for absorption than other foods. But when taken with other foods it economises the use of fat and carbohydrate, which in their turn are stored in the body, the carbohydrate as glycogen, and fat in the tissues. As alcohol does not require digestion it is in a sense superior to other foods.

Although it cannot replace protein, alcohol will, under certain conditions, spare the protein in the same way as fat. It has been experimentally shown (Rosemann and Neumann) that on an ordinary diet the nitrogen equilibrium is maintained at a constant level, but if part of fat is withheld from the same diet, nitrogen excretion increases, showing destruction of protein, *i.e.* proteins are being drawn upon to supply the energy required in place of fat. If, however, an amount of alcohol chemically equivalent to the omitted fat is added to the diet, nitrogen equilibrium again becomes established. It is thus evident that alcohol is able to spare protein in the same way as the fat, and can thus prevent tissue waste. Alcohol therefore may be regarded as a food in the sense that it will, when given with other foods, replace carbohydrate and fat for a short time and would supply energy and spare protein and prevent tissue waste. But the value of alcohol as a food is limited because the supply of energy is fixed and cannot be adjusted according to the needs of the body, nor can it be increased to meet sudden emergency, because it cannot be stored in the body like fat or carbohydrate as reserve.

Nervous system —In moderate doses, the action of alcohol on the nervous system is that of **apparent stimulation** which is soon followed, according to the quantity used, by that of **sleep and coma**. In small doses it produces a feeling of mental and physical well-being. Imagination becomes brighter, feelings elevated, intellect clearer (highest functions of the brain), senses more acute, bodily activity more pre-

dominant, and some of the lower appetites sharpened. If the dose is increased, judgment fails while the imagination, emotion, and power of speech are still excited, then the imagination and will power give way. If indulgence is continued further, symptoms of acute alcohol poisoning appear so that the mental balance is lost. He talks, laughs, sings or cries without restraint, but gradually he loses control over these functions also, thus the speech becomes thick, incoherent and at last suspended. The muscles next get affected, at first the delicate movements, such as writing, playing on the piano, etc., are abolished. But if the dose is very large there is complete insensibility, narcosis, muscular relaxation with involuntary passage of urine and stool and subnormal temperature. The breathing becomes stertorous with cyanosis, finally the patient dies from respiratory paralysis. It will be seen that in its progressive action either of stimulation or of depression it follows the law of dissolution (*see* page 140). But the explanation of these effects is not very clear. Binz and his followers maintain that alcohol first stimulates the nerve cells in the central nervous system and subsequently depresses them, and we have already noticed that in small doses it stimulates the higher functions of the brain which functions are subsequently depressed by larger doses. The other view is that of Schmiedeberg. He holds that alcohol acts as a narcotic from the very commencement and the symptoms of stimulation are the effect of the depressant action on certain higher cerebral functions which normally exert a controlling influence, *viz.* the will and self-restraint. This latter view seems to have more supporters and is generally accepted.

Observations have shown that when alcohol is taken without any exhilarating company many of the manifestations are not elicited. In fact the effects depend upon the nature of the environment and on the inherent mentality of the individual, and would produce quite diverse symptoms on different persons and different effects on the same individual under different conditions. Owing to a certain degree of freedom from restraint, the person will be talkative, boisterous, sentimental or melancholic according to the individual peculiarities.

Circulation.—The reflex effect of alcohol in stimulating the circulation and respiration has already been mentioned. But its action after absorption is uncertain and depends on several factors, *viz.* the dose and concentration, the mode of administration and the condition of the individual. After absorption the vessels of the skin dilate giving rise to a feeling of warmth but those of the internal organs, specially of the splanchnic area, constrict so that it allows more blood to pass through the vital organs chiefly the heart and the central nervous system, and causes a rise of blood pressure.

The normal heart muscle is not affected in small doses, but when exhausted it may be stimulated. During the stage of intoxication the pulse is accelerated due to excitement. The output of the heart, the force and amplitude of the pulse, and the circulation in general are more or less improved. When large doses are taken, the stimulant effect is followed by depression with fall of pressure due to dilatation of the splanchnic vessels replacing the constriction of the first stage. It should be noted that the heart which is stimulated at first is more exhausted than before after the temporary effect has passed off. Large doses do not stimulate the heart at all, in fact the heart is paralysed both reflexly and after absorption.

Respiration.—We have already observed that the medullary centres are affected last, in fact, respiration, though it becomes stertorous, does not stop even after the patient has become completely unconscious and all the reflexes are abolished. The respiratory centre is stimulated reflexly from the stomach before absorption however, but whether the centre is stimulated after absorption has been the subject of much controversy, and it is generally agreed that although the centre is not stimulated to any marked degree in small doses it is not depressed except after large doses and that even as a late symptom of poisoning. In fevers and diseases of the lungs like pneumonia, the respiration is slowed and steadied not from any direct action on the centre but through its narcotic effect it lessens excitability and anxiety and appreciation of distress.

Muscular system.—It was formerly believed that alcohol increases the physical power for more work, but later observations have shown that it is not so, although in the beginning the muscular strength increases through increased circulation in the nervous system. This is soon followed by diminution of working power, so that the total amount of work done is less.

Alcohol is taken after severe muscular work not for any stimulant effect, but for its depressing effect on the nervous system, which gives a feeling of comfort and well-being while forgetting fatigue. In fact observations made with ergograph have shown that muscular work is not increased but it lessens the appreciation of fatigue so that the workers think that they have done more work, or perhaps owing to this fact may do more work, not from increased capacity but from lessened appreciation of tiredness.

Skin and kidneys.—Alcohol is a mild diaphoretic due partly to the dilatation of the skin vessels and partly to its effect on the sweat glands. This dilatation gives rise to a feeling of comfort and heat. Alcohol therefore is a mild antipyretic and is used to promote sweating after an exposure to cold to avert the onset of catarrhal infection.

But the diaphoresis depends on the renal excretion and in cold climates instead of diaphoresis there is diuresis, and the large quantity of water taken with alcohol is excreted by the kidneys. There is also some dilatation of the renal vessels. If alcohol is taken in large amounts a portion is excreted in the urine unchanged. Gin has a greater diuretic effect than other spirits. Prolonged use produces changes in the renal cells and may give rise to chronic nephritis.

It should however be noted that after very large quantities of alcohol the dilatation of the cutaneous vessels may proceed to such an extent that death may follow from excessive radiation of heat, though the drinker may feel a sense of temporary warmth in the beginning, if his vessels were contracted previously from cold air.

Temperature —Alcohol acts as a mild antipyretic, by increasing the heat loss (*a*) from dilatation of the cutaneous blood vessels thereby producing increased perspiration and radiation, although it causes a subjective feeling of warmth; and in larger doses (*b*) by acting on the heat regulating centre which is rendered less sensitive. It is therefore harmful to take alcohol during exposure to cold, for although there is a subjective sensation of warmth it lessens the power of the body to conserve heat.

Tolerance —Long continued use produces tolerance so that a patient can take quite a large dose without showing any of the symptoms of intoxication. To these persons it is necessary to use large doses to produce the desired effect. Two factors are concerned in the production of tolerance, viz. capacity of the tissue to oxidise alcohol as soon as it is absorbed, and that the brain reacts less than normally.

Absorption and elimination. —Taken by the mouth about 25 p.c is absorbed by the stomach, the rest is passed into the intestine to be completely absorbed and no alcohol reaches the colon. It is broken down entirely in the body, only from 2 to 10 p.c. being excreted by the breath, skin and urine. Mellanby has shown that it appears in the blood within five minutes after administration by the mouth, and that it reaches highest concentration within an hour and a half.

It is generally believed that a concentration of 0.2 to 0.4 p.c in the blood or urine implies moderate intoxication, over 0.4 p.c. marked intoxication in most, and over 0.5 p.c in all. The concentration of alcohol in the blood of living animals in deep narcosis is 0.7 p.c. A percentage of 0.8 or over means death.

Acute toxic action. —When an excessively large dose is taken the stage of stimulation is soon followed by that of narcosis with impairment of sensation and motion, etc., already described under nervous system. Death is relatively rare, but may occur suddenly from reflex stoppage of the heart, or the coma may become deeper and death may occur from paralysis of respiration or the heart, or from pulmonary

œdema, generally within twenty-four hours. If coma continues for more than twelve hours recovery is exceptional.

Treatment.—Evacuate the stomach by pump or emetics, such as apomorphine. If the patient cannot swallow, coffee with ammonia may be introduced with the pump after stomach washing. Inhalation of CO₂ with oxygen for respiration and cyanosis; strychnine subcutaneously, or caffeine. Subsequent headache and nervousness require bromides, feeling of depression and gastritis should be treated with bicarbonate of soda, and sal volatile.

Chronic toxic action or "Alcoholism" is induced by prolonged alcoholic indulgence. Insomnia, muscular tremor, and gastric disturbance are the early symptoms. Gastritis, peripheral or multiple neuritis, cirrhosis of the liver causing ascites, chronic interstitial nephritis causing anasarca, dilatation of the heart, gout, nervous disorders, such as delirium tremens, epilepsy, paralysis, insanity, etc., are the diseases which afflict confirmed drunkards. Chronic alcoholics exhibit a train of symptoms which are grouped under the heading of *Karsakoff's Psychosis*, in which emotional tendencies, untruthfulness, indiscretion, mental confusion with loss of memory for recent events, and loss of idea of space and time are often present. Generally they are thin, but a few, especially those who drink beer, get fat. They cannot withstand well any serious illness, such as pneumonia, and are particularly liable to attacks of phthisis. Gin drinkers mostly suffer from cirrhosis of the kidneys and liver.

THERAPEUTICS OF ALCOHOL

Externally.—Application of an alcoholic lotion with a piece of cloth and allowing free evaporation, is useful in some forms of headache, acute inflammation, as sprains, bruises, etc., and prevents bed sores and cracked nipples by hardening the skin. Sponging with alcoholic lotion relieves itching of urticaria. Pure alcohol or brandy when rubbed into the body checks excessive perspiration and brings back warmth to the surface in collapse and syncope. Liniments containing alcohol are used as counter-irritants in stiff joints, chronic rheumatism, bronchitis, pneumonia, etc. Absolute alcohol is sometimes injected into nerves in cases of sciatica and neuralgias, when it relieves the pain by causing degeneration of the particular nerve, and the pain does not recur till the nerve has regenerated again, which takes several months.

Alcohol (70 p.c.) is used for washing the skin and the hands before operation, for sterilising delicate instruments, and syringe for hypodermic injection. Concentrations above 80 p.c. and below 60 p.c. are almost inactive since they do not penetrate proteins of bacteria readily.

Internally. Mouth.—As a local astringent, anodyne and antiseptic, it is used in many mouth and throat diseases. Undiluted brandy held in the mouth relieves toothache and the pain of follicular tonsillitis. The latter disease is also benefited by its astringent and antiseptic properties.

Stomach.—As a digestive stimulant, alcohol may be given in small doses just before or during meals in the following class of cases :—

1. Convalescents from acute illness with weakened appetite and digestion.

2. Patients suffering from chronic wasting diseases.

3. Town-dwellers leading a sedentary life

4. Old and overworked persons.

A good peg of whisky or brandy with hot water often relieves gastric spasms. Fainting, syncope, or threatening collapse may be averted by a single large dose of brandy or whisky by reflexly stimulating the circulation. Diarrhœa in the beginning may be checked by a stiff dose of brandy.

Heart.—As a **cardiac stimulant**, brandy or whisky is used in the threatening cardiac failure due to shock, hæmorrhage, febrile and other diseases. Its value in shock is doubted by many careful observers; and it is very difficult to assess the value of a drug in this condition. It is possible that it benefits by lessening anxiety and pain provided the patient is conscious. As a diffusible stimulant it acts purely reflexly, by increasing the pulse-rate, blood-pressure and the respiration. This effect being of short duration it is used mainly as an emergency drug. The narcotic effect is also of value, since the psychic centres are not so easily excited and the medullary centres are less subject to dangerous shock.

Nervous system.—Alcohol must be used with great caution in depressed conditions of the nervous system lest a bad habit be induced. Most nervous diseases do not require any alcohol. In some cases of insomnia, hysteria and neuralgia, alcohol no doubt affords temporary relief, but it must, if possible, be avoided for fear of generating intemperance. As to the use of alcohol in delirium tremens opinions differ. It should be withdrawn in the course of a few days. A sudden stoppage will precipitate the onset of delirium tremens. As a hypnotic alcohol may be used in mild insomnia due to overwork or mental strain at bed-time, either alone or as an adjuvant to other simple hypnotics.

Kidneys.—Gin is a powerful diuretic because it contains juniper which is also a diuretic. As alcohol is eliminated by the kidneys, and is an irritant to the mucous membrane of the urethra, it should be avoided in gonorrhœa, gleet, etc.

Fevers.—Alcohol was formerly almost invariably used in acute febrile diseases as a respiratory and circulatory stimulant, but its use has become very limited in recent years; in fact most cases of fevers do well without it. Experience alone will guide the practitioner when and where to use wines. It is only in exceptional cases and for limited periods that alcohol may be necessary to enable a patient to turn a critical corner. Its use is specially indicated in **exhausting fevers**, like typhoid, pneumonia and septic fevers. The beneficial effects are due not only because it acts as a food, but because it stimulates digestion of other foods. In wasting and exhausting diseases it tends

to prevent excessive tissue waste and by acting as a narcotic allays nervousness and promotes sleep. Alcohol thus maintains the strength and nutrition of the patient, increases the output of the exhausted heart and makes it slower, regular and stronger. The tongue becomes moist, respiration less hurried, and in place of delirium the patient becomes quiet, free from excitement, and sleeps better so that strength is maintained. If alcohol fulfils these objects then it is doing good and its use should be maintained, if not it should be discontinued. The action should be carefully watched to get the stimulant effect and not the depressant one.

Prescribing hints.—It must be borne in mind while ordering alcoholic beverages that the effects produced are modified by various circumstances, such as (*a*) the amount of volatile ethers they contain; this is of more importance than the actual alcoholic strength; (*b*) the degree of their dilution with water; (*c*) the age, toleration and habits as regards alcoholic drinks of the patient, (*d*) the amount of exercise taken by him; (*e*) the condition of his stomach, whether empty or full; (*f*) the condition of the liver and the excretory organs, especially the kidneys; and (*g*) the nature of the diseases for which they are given.

In many exhausting febrile or other diseases, patients can consume without intoxication a large amount of alcohol, even as much as one pint of brandy per diem. Sparkling wines (carbonic acid) facilitate absorption and produce a quicker action. Old brandy, whisky or port should be preferred as they contain less injurious ingredients. Children tolerate relatively larger quantities. In chronic diseases wines are more useful, but are liable to undergo fermentation in the stomach and are not so well-borne by some patients. Red wines usually disagree when there is hyperacidity. Owing to the presence of malt and diastase, beer produces obesity and aids digestion of carbohydrate foods.

Different varieties of wines should not be given at the same time, as they derange digestion. Small quantities in repeated doses with some easily digestible food are the best method of administration. Debilitated persons do well if an alcoholic drink is given an hour before food. Champagne, port, strong claret or beer may produce burning and aching of the rectum, and new and inferior brandy or whisky headache, because the latter contains fusel oil, furfural and many injurious aldehydes.

It should be avoided where there is gastric irritation and when the kidneys are diseased on account of its effect on the renal epithelium.

For continuous use $1\frac{1}{2}$ ozs. of pure alcohol is all that can be utilised as a food in the human body daily. Roughly, $1\frac{1}{2}$ ozs. of pure alcohol equals 8 ozs. of whisky or brandy,

which is equal to $1\frac{1}{2}$ peps, or is equivalent to 7 ozs. of sherry, 15 ozs. of champagne, claret or white wine.

2. General Anæsthetics and Narcotics

Narcosis is a "physiological condition in which the normal responsiveness or automatic activity of the living system—organism, tissue or cell—is temporarily decreased or abolished." Drugs which produce unconsciousness are called *narcotics*, and unconsciousness however produced is always accompanied by some degree of reflex inhibition. Hypnotics in large over-doses often act as narcotics, i.e. cause a profound degree of unconsciousness. The difference between the two being one of degree. Consciousness is the function of the cerebral cortex. The rapidity of the onset of narcosis varies but the degree increases in a regular way with the amount given. In very small doses they produce a tendency to quietness, while in larger amounts they give rise to drowsiness, sleep, stupor, and finally loss of consciousness and coma. Narcotics therefore are used either to induce sleep or to produce surgical anæsthesia.

The narcotic effect of a drug persists as long as it remains in the blood in sufficient concentration, and no narcotic drug is known to get itself fixed in the brain cells so as to exert any late effects after the drug has been excreted from the general circulation. *Volatile narcotics* being rapidly absorbed and rapidly excreted by the lungs exert only a temporary effect; whereas the *non-volatile narcotics* are excreted *via* the kidneys only to a limited extent and therefore maintain their effect for a longer period. These are therefore largely used to maintain a state of sleepiness and mental dullness.

Many views have been advanced from time to time to explain the way these narcotics act, but still we are far from any definite knowledge as to their mode of action. Since the chemical structure of the different narcotics have very little in common between them to explain their common effect, attempts have been made to explain their action as the result of some physical effect on the function of the brain cells exercised from outside rather than a chemical union with any of its components. The chief narcotics are formed by the union of one or more hydrocarbon groups, e.g. ethyl or amyl, with polar groups, such as $-\text{OH}$, $-\text{CO}$, $-\text{NH}$, $-\text{CO}-\text{NH}_2$. The hydrocarbon group is lipid soluble, while the polar group is water soluble. In other words it is the physical property of a drug rather than its chemical affinities which determine the narcotic effect. Mayer and Overton have therefore advanced the theory of a close relationship between the narcotic action of these drugs and their relative solubility in oil as compared to water, i.e. a close parallelism between narcotic efficiency and partition coefficient, i.e.

$$\frac{\text{solubility in fat}}{\text{solubility in water}}$$

The higher this coefficient, the more powerful the narcotic action. They hold that all narcotic drugs are more soluble in fats and lipoids than in water. Thus when a narcotic drug circulates in the blood, it leaves the blood and since the nerve cells are rich in lipoids it accumulates in the brain and so alters the physical condition of the brain lipoids and interferes with their normal activity as to produce an anæsthetic effect. This effect is regarded as the function of the narcotics. This theory however applies to narcotics of the aliphatic series, *viz*, chloroform, ether, chloral hydrate, etc., while morphine and other basic and saline narcotics like bromides, do not obey this law; moreover, the peripheral nervous system though rich in lipoids is not affected by aliphatic narcotics.

Since it is known that deprivation of oxygen, as in asphyxia, causes anæsthesia or narcosis, and that narcosis is followed by

diminished oxygenation, Verworn and his associates maintain that deficiency of oxygen produces anæsthesia. They argue that narcotics render the oxygen carriers of living tissues incapable of carrying oxygen. This view however is not generally accepted on the ground that diminished oxygenation may not be the cause of narcosis, but an effect of all narcosis which by suppressing irritability depress oxidation.

Traube has shown a close relationship between the narcotic power of a drug and its power to lower surface tension to water. Here is again a similar parallelism between the surface tension effect and the partition co-efficient, and it is not possible to say as to which property is the determining factor in narcosis. It is possible that both the factors participate to a varying extent in different tissues.

The real laws which govern the action of narcotics are not quite clear, and many carefully prepared substances have been found to possess totally different action from that anticipated. The reason why one drug acts as a narcotic than another is in many instances as obscure as is the cause which produces sleep or physiological narcosis.

The drugs of this group when used in sufficient concentration produce unconsciousness, muscular relaxation and abolition of all reflexes and pain so that operations can be performed without the patient feeling any pain. Most of these drugs belong to the aliphatic group, and being very volatile, some gaseous, they are rapidly absorbed by the lungs, therefore they are administered by inhalation. They should be quickly eliminated from the system so that the patient will regain consciousness as quickly as possible after the anæsthetic is discontinued, at the same time they must produce these effects without depressing the vital centres dangerously, or causing any permanent damage to the central nervous system. The study of general anæsthetics means a knowledge of their toxicology, the patient being drugged into a state of narcosis approaching collapse.

Within recent years certain non-volatile substances are being extensively used for the production of general anæsthesia and narcosis. Those that are extensively used for the purpose are avertin and the rapidly acting barbiturates, viz. evipan sodium, pentothal sodium (which contains sulphur), pernocton (which contains bromine), sodium amytal and nembutal. These are all soluble in water and are administered some by the mouth, others by the rectum, by intramuscular injection or by the intravenous route, the object being to produce partial narcosis, the anæsthesia being completed with some volatile or gaseous anæsthetic, or alternately with a spinal or local anæsthetic. But all are not suitable for all the routes. They belong to two groups, viz.

- (1) Alkaloidal narcotics, viz. hyoscine and morphine ;
- (2) paraldehyde, avertin, derivatives of barbituric acid, and sulphate of magnesium

These are used either for the production of general anæsthesia, or as basal narcotics preliminary to the use of volatile anæsthetics.

C L O O F O U

Chloroform. (Chlorof). CHCl_3

Source.—It is *trichloromethane* to which 1 to 2 p.c. v/v of dehydrated alcohol has been added. Prepared by the action of chlorine in the presence of alkali, on ethyl alcohol, industrial methylated spirit, or acetone.

Characters.—A colourless, volatile liquid ; odour, characteristic ; taste, sweet and burning. *Soluble* in 200 parts of water, miscible with dehydrated alcohol, with ether, fixed and volatile oils, and with most organic solvents. Sp. gr. 1.485 to 1.490.

N.B. If exposed to air and light pure chloroform is gradually oxidised becoming contaminated with a very poisonous carbonyl chloride (phosgene) and with chlorine. This decomposition is retarded by the addition of a small percent. of alcohol.

B.P. Dose.—1 to 5 ms. or 0.06 to 0.3 mil.

OFFICIAL PREPARATIONS

1. Aqua Chloroformi —0.25 p.c. B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mils.
2. Spiritus Chloroformi. *Syn.*—*Chloric Ether*.—5 p.c. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.

NON-OFFICIAL PREPARATIONS

- 1 Tinctura Chloroformi et Morphine Co—A substitute for chlorodyne. Contains chloroform $\frac{3}{4}$ m, morphine hydrochlor $\frac{1}{16}$ gr, acid hydriocyan dil. $\frac{1}{2}$ m in 10 ms *Dose*—5 to 15 ms or 0.3 to 1 mil
- 2 Chloroformum Camphoratum, B P C—Camphor 2, chloroform 1 Anodyne in *toothache*
- 3 Tinctura Chloroformi Co, B P C—Chloroform 10, alcohol (90 p c.) 40, tinct. cardam co 50 *Dose*—15 to 60 ms or 1 to 4 mils

PHARMACOLOGY OF CHLOROFORM

Externally—Chloroform when allowed to evaporate constricts the local blood vessels and paralyses the peripheral sensory nerves, and is a local anæsthetic. If the evaporation is prevented, or if it be rubbed into the skin, it causes redness and even vesication. It is an irritant, more powerful than ether, a general protoplasmic poison, and a powerful antiseptic.

Internally.—The same irritant action is observed in the mouth and stomach when chloroform is taken internally. In diluted solution it has a warm sweetish taste and acts as a pleasant carminative and stomachic. It produces a sensation of warmth in the epigastrium and increases the vascularity and secretion of the stomach. Vomiting often accompanies anæsthesia and is central.

Heart and circulation.—Chloroform is quickly absorbed by the lungs and in concentrations used in anæsthesia depresses the muscles of the vessels, the splanchnic vessels being more affected than those of the extremities. It also depresses the vaso-motor centre. As a result of dilatation of the vessels and the depressed condition of the heart the blood pressure falls. The skin becomes pale and cold, pulse soft, slow but regular, although there is quickening during the early stage from nervousness. Ordinarily the vaso-motor paralysis dominates and the heart beats efficiently even when the vaso-motor centre is paralysed.

The heart is very sensitive to chloroform, and experiments with isolated heart show that small amounts produce, after a momentary slowing, depression, rendering the beats smaller and ineffective. A concentration of 0.05 p.c. of chloroform in the perfused fluid will arrest the heart. It

is therefore a direct poison to the cardiac muscle. In prolonged anæsthesia the heart is affected directly, supplemented by low blood-pressure and asphyxia. During anæsthesia the heart may stop suddenly through rapid absorption of concentrated vapour and reflex vagus stimulation. The cause of sudden failure of the heart has been the subject of much controversy. It may occur in the early stage of the anæsthesia, or when the inhalation is irregular, or even after the inhalation has been stopped. Since it does not occur if the vagi are cut or an injection of atropine is given, it has been suggested that the stoppage is due to inhibitory stimulation. Others, chiefly Levy, explain it as the result of fibrillation brought on by excessive irritability of the muscle from chloroform vapour. It is possibly due to excessive sympathetic stimulation acting on an already irritable heart, or to an increased secretion of adrenaline.

Respiration.—In the early stage the respiration is as a rule fairly regular, but deeper and quicker from stimulation of the centre; this is followed by depression of the respiratory centre. If the inhalation is given in large amounts the breathing becomes irregular from choking sensation and local irritation. During the stage of excitement it becomes more irregular, the patient holds his breath and then takes a few deep gasps allowing a large quantity of concentrated vapour into the blood. During the stage of anæsthesia the breathing becomes regular, though noisy, shallow and slow. If the administration is still prolonged it becomes stertorous and quick. The respiration may be temporarily stopped reflexly through irritation of the 5th nerve, *i.e.* through nasal mucous membrane. Reflex closure of the larynx, accumulation of mucus and saliva may also interfere with respiration, and anæsthesia of the larynx may lead to suction pneumonia, which is more common with ether than with chloroform. Direct irritation, hæmorrhagic emboli or impurities in the anæsthetic used may also contribute to the formation of pneumonia.

Blood—Both ether and chloroform when applied to drawn blood cause hæmolysis but this effect is observed in a minor degree in life. Owing to the diminution of plasma there is polycythæmia, but the hæmoglobin is reduced. In deep anæsthesia fibrinogen disappears from the blood thus diminishing its coagulability. This effect is possibly due to derangement of the liver and disappears with its repair.

Eye.—Its effect on the eye varies in different stages and depends upon the amount used. At first the pupil is dilated from stimulation of the sympathetic, though light reflex remains intact. Later there is contraction from stimulation of the oculo-motor centre and paralysis of the sympathetic. During profound anæsthesia the pupils dilate from paralysis of the centre and the reaction to light is also lost. This

implies either (a) overdose, (b) asphyxia, or (c) reflex from operative procedure.

Kidneys—During anæsthesia the secretion of urine is diminished. Albumin appears, and in some cases fatty degeneration and permanent inflammatory lesions of the kidneys have been observed.

THERAPEUTICS OF CHLOROFORM

Externally—As a local anodyne, chloroform may be combined with liniments of aconite and belladonna (A. B. C. liniment) and applied in myalgia, lumbago, chronic rheumatism, etc. If counter-irritation is required the liniment may be sprinkled over a piece of cloth or lint and covered with oiled silk.

Internally.—A pellet of cotton wool soaked in chloroform and introduced into the cavity of a painful carious tooth relieves toothache. One or two drops may check vomiting, sea-sickness and flatulent distension. In diarrhœa or in the beginning of cholera spirit of chloroform may be usefully combined with opium or other astringents. Chlorodyne is a useful remedy in these cases. It is also useful in intestinal and other colics.

A deep hypodermic injection (10 ms.) near the sciatic nerve relieves sciatica

ÆTHER

Ether. Ethyl Oxide. $(C_2H_5)_2O$

Syn.—Ethylic Ether; Sulphuric Ether.

Source—Obtained by distilling a mixture of ethyl alcohol and sulphuric acid, rectifying the distillate.

Characters.—A colourless, transparent, very mobile liquid; odour characteristic; taste, sweet and burning. Very volatile and inflammable. Sp. gr. 0.720 to 0.724. *Soluble* in 8.5 volumes of water, miscible in all proportions with alcohol (90 p.c.), chloroform, fixed and volatile oils.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

OFFICIAL PREPARATIONS

1. **Æther Anæstheticus.** *Syn*—*Æther Purificatus*.—Possesses the characters of ether. Sp. gr. 0.720.

2. **Spiritus Ætheris.**—Contains 33 p.c. ether. **B P. Dose.**—15 to 60 ms. or 1 to 4 mils. Enters into.—Tr. Lobeliæ Ætherea.

NON-OFFICIAL PREPARATIONS

1 **Spiritus Ætheris Co** *Syn*—*Hoffmann's Anodyne*—Ether 137.5 ml, alcohol (90 p.c.) 1950.0 ml, sulphuric acid 900.0 ml, water 37.5 ml, sodium bicarb *q.s* *Dose*—20 to 40 ms or 1.3 to 2.6 mils

2 **Injectio Camphoræ Æthereæ, B.P.C.** *Syn*—*Curschmann's Solution*.—Camphor 20 gm, ether 30 ml, olive oil to 100 ml *Dose*—4 to 15 ms. or 0.25 to 1 ml

PHARMACOLOGY OF ETHER

Externally.—Being extremely volatile, ether cools the skin and even freezes the part so that if applied as a spray

it produces local anæsthesia. The cooling is followed by burning. If evaporation is prevented, it acts as an irritant and even vesicant. It is a powerful antiseptic.

Internally.—It produces burning, a disagreeable and characteristic taste in the mouth and reflexly stimulates the secretion of saliva. In the stomach it is quickly absorbed, increases gastric secretion, expels gas and acts as a gastric stimulant and carminative. It is also a valuable intestinal antispasmodic and reflexly stimulates the heart.

Heart and circulation.—Whether administered by the mouth, hypodermically or as inhalation, ether stimulates the heart and causes a rise of blood pressure. These effects are reflex through stimulation of the accelerator and vaso-motor centres. The heart is also directly stimulated. In the early stage of the anæsthesia the pulse is quickened and the blood pressure is raised. During anæsthesia the cerebral and skin vessels are dilated but the intestinal vessels are constricted and the pressure remains unaltered. During the paralytic stage the vaso-motor centre is depressed, and the blood pressure falls slowly. The heart remains normal even after the stoppage of respiration.

Respiration.—At first respiration becomes quicker and deeper through reflex stimulation from mouth, stomach and the respiratory passages. Large doses, as when given to produce anæsthesia, depress the respiratory centre, death being due to asphyxia from respiratory paralysis.

Uterus.—Moderate anæsthesia has little effect on the uterine contractions, although cases of death of the fœtus under ether or chloroform during labour are on record. This may be due either to a direct action on the fœtus or to asphyxia from low maternal blood pressure.

Kidneys—During the anæsthetic stage the secretion of urine is diminished from constriction of the renal vessels; after this stage is over there is profuse diuresis. Albumin appears in the urine, which however soon passes off, though nephritis with albumin and even blood in the urine may appear in some cases.

THERAPEUTICS OF ETHER

Externally —For superficial minor operations, ether used as a spray produces sufficient anæsthesia for the purpose. As this effect does not extend into the deeper tissues, it is not suitable for deep surgical operations. It is used as an antiseptic for infected wounds.

Internally.—As a carminative and antispasmodic, ether is useful in some forms of dyspepsia, gastrodynia, and intestinal cramps. Hoffmann's anodyne is an excellent combination for the relief of intestinal and biliary colic, and in hiccough when used with ice.

Heart and lungs.—It is a valuable cardiac and respiratory stimulant when given by the mouth (10 to 40 ms.) or hypodermically (10 to 40 ms. dissolved in olive oil) in syncope, fainting and cardiac failure from any cause.* Its effects are transient and it has to be repeated. It is also useful in angina, spasmodic bronchitis, and whooping cough. In the latter disease it is given intramuscularly in doses of 1 c.c. up to the age of 7 or 8 months, repeated daily or given on alternate days. But the pain and danger of necrosis are serious drawbacks to its use. It is given to tone up and allay the irritability of the heart in delirium tremens.

ETHER AND CHLOROFORM AS GENERAL ANÆSTHETICS

Both ether and chloroform when inhaled produce general anæsthesia by their action on the central nervous system. This action may be conveniently described under *four stages* as follows:—

First Stage or that of **imperfect consciousness**.—This begins with a feeling of warmth on the surface, sounds in the head, flashes of light before the eyes, choking or suffocation, or sometimes cough (especially if the vapour is concentrated), and confusion of ideas. Sounds are faintly heard, questions are imperfectly answered, and pain, if present, is not much felt, indicating a blunting of the general sensibility.

Second Stage, or that of **general stimulation**.—The patient is no longer conscious of external impressions, but according to temperament, he may sing, cry, shout, or struggle (hence some authors call this “the struggling stage”). At times the struggling is so hard that the patient holds his breath, the face becomes livid, the eyes protrude and the jugular veins distend. Almost coincidently the lower centres are stimulated; the pulse becomes frequent, the heart and large vessels throb, respiration becomes quickened, blood pressure rises and the pupils become slightly dilated through stimulation of the sympathetic.

Third Stage, or that of **anæsthesia**.—This is characterised by the *paralysis of the nerve-centres which have previously been excited, and the abolition of reflex action and sensation*. If the inhalation is continued, the patient becomes completely unconscious; his limbs quite flaccid, and if one of them is held up it falls like that of a corpse; only a sluggish contraction of the iris follows when the eyes are suddenly exposed to light; the pupils are contracted through stimulation of the oculo-motor centre and paralysis of the sym-

*R

Sp. ammon. aromat.	ms. 30
Sp. ether.	ms. 20
Sp. chlorof.	ms. 15
Tinct. card co	ms. 60
Aq. camph	ad oz 1

A diffusible stimulant

pathetic, and the conjunctival reflex is completely abolished. The pulse falls in volume and frequency, respiration becomes slow and deep, sometimes stertorous, and the blood-pressure falls from paralysis of the vaso-motor centre. This is the proper stage for operation. 60 to 240 ms. of chloroform is generally necessary to bring about complete anæsthesia.

Fourth Stage, or that of paralysis or collapse.—If chloroform is pushed further, the lowest reflex centres are paralysed, causing a complete loss of muscular tone, so that the patient passes urine and stools involuntarily, and the muscles become completely flaccid. Sometimes the surgeon is obliged to push the inhalation to this extent to enable him to reduce dislocations or to examine abdominal viscera through the abdominal wall. If the inhalation is still continued, the pupils dilate, which is an indication of the commencement of asphyxia and of paralysis of the vaso-motor, respiratory and cardiac centres. It is therefore an important "*danger-signal*." The blood-vessels and capillaries now dilate and the blood-pressure falls to zero. Respiration becomes shallower, weaker and irregular, and often stops before the arrest of the heart. The pulse grows feeble and intermittent, and finally the heart stops in diastole.

Causes of death under chloroform.—There has been much controversy as to whether death takes place from the heart or from the lungs. The two Commissions appointed by the Nizam of Hyderabad came to the conclusion that respiration fails before the heart. But the correctness of this view has been strongly disputed. There are three possible dangers in chloroform anæsthesia :

First, occurring early before the patient is completely under, due to heart failure, caused by (a) *direct toxic action on the myocardium* of concentrated poison. The lung surface of absorption is extensive, hence a very concentrated dose passes into the heart quickly ; (b) *stimulation of the vagus centre*, this may be reflex from nose, larynx, trachea, or from pulmonary irritation by the concentrated vapour ; and is avoided by injection of atropine ; or directly from high concentration which makes the centre hypersensitive ; (c) *increased peripheral resistance* from excessive reflex vasoconstriction ; and (d) *fibrillation of the heart*, due to excessive irritability from chloroform vapour, or to increased output of adrenaline.

Second danger is that owing to the depressing action of chloroform on the heart muscle there is a very small margin of safety between the stage of complete anæsthesia and that of complete paralysis or collapse and it is very difficult to resuscitate the patient. Whereas a concentration of 35 mg. to 100 c.c. of blood will produce anæsthesia, a concentration between 40 to 70 mg. per 100 c.c. is fatal.

Third danger is the well known delayed chloroform

poisoning, which may commence within a few hours to six days after the use of the anæsthetic. The symptoms are those of acute acidosis ; there is persistent vomiting, fatty degeneration of the liver, heart and kidneys, leading to toxæmia, icterus, prostration, coma and death. This is more common in patients suffering from acetonuria, diabetes, cyclic vomiting, rickets and wasting diseases.

Dangers during administration.—Broadly speaking they may arise from two sources, *viz.* (1) failure of respiration, and (2) failure of the heart, as detailed below :—

1. **Death from suffocation may be caused by :—**

(a) *Obstruction of the glottis* by falling back of the tongue or the sucking in of vomited matter or blood.

(b) *Spasm of the glottis* from the inhalation of chloroform vapour, which is either too strong or contains irritating products of decomposition.

(c) *Mechanical impediments to respiration*, due either to (1) *constrained position of the patient* as in obstetric and renal operations ; (2) *pressure of tight clothes or bandages*, or the *assistant's arms* ; (3) *falling in of the lips and alæ nasi*, as in old people who have lost their teeth ; (4) *spasmodic holding of the breath* especially in nervous patients, and during the early stages of the administration.

(d) *Paralysis of respiration* occurs more often from ether than from chloroform, where deaths are due more from cardiac shock. If chloroform or ether is used freely diluted, the respiration stops before the heart, in more concentrated forms the heart continues to beat for a very short time. It is possible that the failure of respiration may be the effect of anæmia of the central nervous system from fall of blood pressure. Weakness of the heart therefore only indirectly affects respiration.

2. **Death from the stoppage of the heart may occur from :—**

(a) *Excessive concentration of chloroform vapour* causing sudden paralysis of the cardiac muscle.

(b) *The shock of operation*, reflexly stopping the heart. This may happen even in trivial operations, especially if anæsthesia be incomplete

(c) *Disease of the heart*. The heart is apt to fail if it is fatty, dilated, or structurally disorganised. Therefore it is risky to administer chloroform to the old, the infirm, the anæmic, drunkards, epileptics and those who suffer from valvular diseases. For them ether is the safest anæsthetic. A C.E. mixture (alcohol 1, chloroform 2, ether 3) or the simultaneous inhalation of oxygen and chloroform vapour may also be resorted to in carefully selected cases.

(d) *Pressure on the carotid sinus*. Since external compression of the carotid sinus stimulates the adventitial sensory nerve-endings and reflexly slows the heart, or sometimes

may cause complete arrest of the heart, it has been suggested that the nerve connections of the sinus and the effect of pressure on it may have some connection with the sudden stoppage of heart under an anæsthetic.

Kemp believes the cause to be a defect in function or substance of the adrenal cortex, with secondary dysfunction of the thyroid.

Recovery from anæsthesia.—The rapidity of recovery depends upon the amount of anæsthetic used and on the duration of administration. If after full anæsthesia the patient is just kept under with a few whiffs now and then, recovery takes place very soon after the administration is stopped. The lowest functions reappear first, the respiration becomes quieter, the eye reflex and deglutition reflex appear next, then after a while consciousness returns. The mental equilibrium is established last. Coughing, retching and vomiting appear with return of consciousness.

Absorption and elimination.—Both ether and chloroform are absorbed and eliminated very quickly from the lungs, only a small part being excreted by the urine. At the beginning the amount excreted, *i.e.* in the expired air is much less than in the inspired air, showing that there is retention of the anæsthetic in the body. They exist in the blood and tissues chiefly in physical solution, and are therefore absorbed and excreted by the alveolar blood in proportion to their concentration in the alveolar air. With ether, light anæsthesia can be obtained at a concentration of 6 p.c. (by volume) of ether vapour, while deep anæsthesia requires 10.5 p.c. by volume. Fatal concentration with ether is 11 p.c. For chloroform, the corresponding concentrations are 1.35 volume p.c. for light anæsthesia, and 1.65 p.c. for deep anæsthesia, and fatal concentration is 2 p.c. (Sollmann). The margin of safety between minimal anæsthetic and fatal dose therefore is greater with ether than with chloroform.

After effects of ether and chloroform.—(a) *Vomiting*, when slight is of no consequence, and is a sign of reaction from shock after operation. Sometimes it may be severe, and may be due to (i) idiosyncrasy or digestive disturbances, (ii) a central effect, and (iii) excessive dose of chloroform. In the early stage vomiting is due to the taste and smell of the vapour.

(b) *Bronchitis and complication of the lungs.*—These occur chiefly from the use of ether which irritates the bronchi, and in susceptible persons may set up bronchitis. It may even cause severe and fatal bronchial complications in persons suffering from pulmonary congestion, bronchitis and phthisis. Sometimes infection may occur from septic inhaler.

(c) *Acid intoxication.*—Administration of any lipoid-soluble anæsthetic reduces the alkali reserve of the blood, specially if the administration is prolonged. The danger is

greater in conditions associated with acidosis, *e.g.* in diabetes, eclampsia, vomiting of pregnancy, acute yellow atrophy of the liver, etc. In these conditions the use of glucose and bicarbonate of soda before starting the operation should be considered.

(d) *Renal irritation*.—In a certain percentage of cases, more with chloroform than with ether, albumin appears in the urine with casts. This usually disappears in persons with healthy kidneys, but in persons with diseased kidneys there may be fatal suppression of urine and occasionally fatty degeneration.

(e) *Troublesome flatulence and post-operative gastric and intestinal paralysis*.—These are more common with ether. The relaxation of the gastric muscles favours dilatation of the stomach and irregular peristalsis, which are responsible for the 'gas pains' so common with ether. Sometimes there may be spastic contraction of the colon with accumulation of gas and fluid above.

Cases unsuitable for chloroform.—Those suffering from anæmia, low blood-pressure, cachexia, angina, weak and fatty heart, Graves' disease, hæmorrhage and adenoids. Diabetics and any condition that favours acidosis, and those suffering from jaundice are also bad subjects for chloroform.

Cases unsuitable for ether.—Those suffering from laryngeal spasm or obstruction, and any disease of the lungs or pleura. Very old age, those suffering from atheroma, aortic aneurism and renal disease, and operations with cautery near the mouth are contra-indications for ether.

Accumulation of mucus or saliva often gives trouble by blocking the air way, and is more marked with ether. This is obviated by giving a preliminary injection of atropine, or by turning the head to one side to help drainage, or by swabbing out the mucus with mops. During the stage of muscular relaxation the falling back of the tongue obstructs the air passage.

Uses of general anæsthetics.—These are chiefly restricted to cases where surgical operations or manipulations are required and which will involve much pain and suffering to the patient. They are therefore used to annul pain and produce unconsciousness. Their field of usefulness has however within recent years become limited owing to our advance in knowledge regarding the different local anæsthetics, and the various improvements introduced with regard to their uses. In fact many operations which were formerly performed under general anæsthesia are now done with local anæsthetics with much success. There are however certain limitations to the use of local anæsthetics. Where complete relaxation of the muscles is essential to the success of the operation, or where any movement on the part of the patient may interfere with the success of the operation, or where we

want to avoid any depressing effect associated with the operation in a nervous patient, chloroform and ether will continue to hold their field. Apart from their uses in surgical operations they may be used under the following conditions:—

1. *To produce anaesthesia of slight degree during labour* with moderate inhalation after full dilatation of the os. Deep anaesthesia is as a rule not required and only prolongs labour.

2. *To relax muscular spasm* during the reduction of dislocations or hernias, the setting up of fractures, or during catheterisation.

3. *For the purpose of diagnosis*, as in the case of young children or hysterical subjects. For the examination of abdominal viscera or to ascertain whether a particular swelling is a real or a phantom tumour.

4. *To relieve the intense pain of certain diseases*, such as biliary, intestinal and renal colics, neuralgias, etc.

5. *To relieve the spasms* of many convulsive diseases, such as tetanus, strychnine poisoning, hydrophobia, eclampsia, chorea, uræmia, etc.

Administration of chloroform.—The essential feature in the administration of chloroform is to avoid the danger of over concentration of the vapour, or of surcharging the blood by too rapid administration.

The following practical hints should be particularly attended to while administering chloroform:—

1. Chloroform should be perfectly pure. The A. C. (alcohol and chloroform) mixture or A.C.E. mixture is only indicated in cases where there is a fatty or weak heart, or where the operation is likely to be a protracted one.

2. All tight clothes about the neck, chest and abdomen should be removed or materially loosened. Attendant's or dresser's hands should not press upon the chest or abdomen while holding the patient.

3. Artificial teeth should be removed.

4. The safest position of the patient is the dorsal decubitus.

5. As the undivided attention of the anaesthetist is essential for the safety of the patient, the operator should not undertake to administer the chloroform and to operate at the same time.

6. Chloroform should be freely diluted with air.

7. An ordinary handkerchief or a piece of lint folded in the form of an open cone within which some absorbent cotton has been stitched is the best inhaler in the absence of Junker's apparatus, which does not allow a greater concentration of chloroform than 5 per cent. If a cone is used it should not be held either too close to or too distant from the mouth and the nose. The proper distance throughout the inhalation is the nearest which does not cause choking, struggling or holding of breath.

8. If the patient is weak, a small dose of brandy or whisky may with advantage be given before the inhalation is begun. A nervous patient should be brought into a calm state of mind as far as possible and an injection of morphine may be considered (*see* Basal Narcosis).

9. If lint is used, not more than 20 or 30 ms. should be sprinkled on to it at a time. Some anaesthetists prefer to commence with double this dose, so as to lessen the period of excitement.

10. Pay particular attention to the breathing, as most of the accidents are caused by respiratory failure. Irregularity of breathing is generally caused by insufficiency of air, which makes the patient struggle, or hold his breath.

11. No operation should be commenced until the patient is under complete anæsthesia, as shown by the absence of the corneal reflex. The administration should never be pushed to the stage of stertorous breathing and complete relaxation of muscles, except when it is absolutely necessary as for the reduction of old-standing dislocations.

12. Directly the corneal sensibility is lost or respiration becomes stertorous, the inhalation must be suspended. In case the stertor comes on while the cornea is still sensitive, the inhalation should not be proceeded with, as it invariably happens that the cornea becomes insensitive within a few seconds afterwards.

13. The patient's head should be turned to one side, the lower jaw depressed and the tongue drawn forward if necessary during vomiting, so that no vomited matter may enter the larynx. Should this accident happen laryngotomy must be at once performed.

14. Special care should be taken during an operation on the mouth to prevent any blood flowing down into the larynx. Full anæsthesia may be maintained by introducing chloroform vapour into the post-nasal space through a soft catheter connected with the Junker's inhaler; or by injecting morphine subcutaneously before the inhalation.

15. Lividity of the face and deep stertor should at once be controlled by raising the shoulders, opening the mouth, and pulling out the tongue. If breathing threatens to stop or stops altogether, artificial respiration should immediately be commenced and at the same time fingers may be thrust under the ribs to mechanically stimulate the heart. Artificial respiration should be maintained for at least an hour or so, and if there be any sign of returning life, it should be continued for several hours. In addition to the above measures, injection of strychnine, ether, and brandy hypodermically; the inhalation of carbon-dioxide and oxygen, bandaging of the limbs, compression of the abdominal aorta and lowering of the head should all be tried.

Preparation of the patient.—During an emergency it is not possible to prepare the patient adequately, and it is surprising that as a rule no untoward result follows the use of an anæsthetic. Even under normal conditions the drastic methods of preparation followed before are avoided. The patient is given a preliminary purge, preferably castor oil, 36 hours before operation, and an enema on the evening before. Sometimes a rectal wash is given a few hours before the operation, but this weakens the patient and is not given except in cases of rectal operation. The patient should be kept on light food on the previous day, and no food is given on the morning of the operation to keep the stomach empty and avoid vomiting. A cup of tea and a slice of toast may however be given if necessary. Glucose or some form of sugar is of great service to replenish the carbohydrate reserve of the body and as a *preventive against post-anæsthetic vomiting and acidosis*. An injection of atropine is given as a routine method to prevent excessive perspiration, secretion of mucus and reflex vagus stimulation. It is more indicated when ether is used and should be given in full doses.

Treatment of untoward symptoms. (a) *Cyanosis*.—When due to obstruction of the air way, as by excessive secretion, falling back of the tongue, etc., this should be rectified without delay. When due to respiratory weakness, it demands immediate withdrawal of the anæsthetic, use of artificial respiration and administration of respira-

tory stimulants, e.g. atropine, strychnine, or caffeine. It is however very doubtful if any of these drugs are of any use when the circulation is so feeble that the drug cannot reach the vital centres to stimulate either the respiratory centre or the heart.

(b) *Weak and irregular pulse* should be treated by stoppage of further anæsthetic and administration of saline, either per rectum or intravenously, depending upon the urgency of the case.

(c) *Collapse*.—(i) In ether anæsthesia, whatever may be the stage of operation, it should be suspended and the patient put into Trendelenburg position. If from chloroform, keep the body level.

(ii) Lungs should be slowly and rhythmically inflated with CO₂ and oxygen (10 p.c. and 90 p.c.), or with pure oxygen.

(iii) Hot blanket to keep the body warm, and if necessary, the limbs may be bandaged from fingers upwards.

(iv) Injection of atropine or caffeine in ether anæsthesia, and cardiac stimulants in chloroform collapse, e.g. camphor, coramine or cardiazol.

(v) Heart failure may be treated with injections of strychnine, camphor or glucose. But since all these drugs act in diverse ways, it has been suggested that the stimulation caused by the needle brings on recovery. Cardiac massage may also be tried. Since adrenaline favours fibrillation, it should not be used in cardiac syncope.

Carbonic acid gas in anæsthesia.—This gas being the natural and efficient respiratory stimulant is of great use to the anæsthetist, and when used with oxygen it hastens the induction of anæsthesia by stimulating breathing. At the end of the anæsthesia it will help the elimination of the anæsthetic and thus lessen post anæsthetic complications. Besides preventing respiratory failure it counteracts shock. It is used in strength of 5 p.c. with oxygen.

Treatment after inhalation.—No food should be given for at least two hours after inhalation. Iced soups or jellies and iced milk with soda water may be given during the next 12 hours. Vomiting may be checked by the sucking of lumps of ice or by a teaspoonful of burnt brandy.

Method of administration of ether.—The routine method is by inhalation either by the open or closed method. The open method is safer but more anæsthetic is required and it takes a longer time to produce anæsthesia. Buxton recommends inhalation of ether with oxygen in cases where the introduction presents difficulties from spasm, cough, holding of breath, struggling with cyanosis, in alcoholics and in persons with weak vitality. Hewitt and Blumfeld advocate the administration of ether 3 parts and chloroform 2 parts by volume by the open method (Skinner's mask) to the exclusion of all other methods on account of its alleged safety and freedom from after effects. Recently ether is given per rectum dissolved in equal volume of olive oil, and may be combined with paraldehyde or chloretone. Ether 2 to 5 oz., olive oil 2 to 4 oz., and paraldehyde 2 to 4 drs. forms a suitable dose for an adult, depending upon the physique and depth of anæsthesia required. This is introduced by a siphon tube 20 minutes before the operation after emptying the rectum with a purgative followed by an enema. An hour before the operation a dose of morphine, or atropine and scopolamine is given. When the operation is over, the unabsorbed portion is siphoned off and the bowel washed out with soap and water enema. This method spares the respiratory tract so that there is less salivary and bronchial secretion and there is less vomiting and nausea. It is especially indicated in operations about the mouth and throat. But the anæsthesia is not under full control, and may be followed by irritation and even hæmorrhage from bowels. A few cases of death have been recorded in children possibly due to overdosage, or to absorption of an excessive quantity from unhealthy condition of the rectum.

Choice of anæsthetics.—There is a wide range of anæsthetics, both

local and general, for the surgeon to make his selection from. The indications for both ether and chloroform have been fully discussed. It is only necessary to point out that in both cases the drug must be pure. Chloroform would have been the ideal anæsthetic if it were safe. It is portable, and least bulky of all the anæsthetics and never fails to anæsthetise. It causes less irritation and less feeling of suffocation. On the other hand ether is rather more than twice as safe as chloroform. Where however irritation of the air passages is apprehended and muscular relaxation is required, chloroform should get the preference. For short operations the choice should be for gas and ethyl chloride, and for prolonged operation, gas, oxygen and ether. The choice of an anæsthetic will depend upon (1) the patient's physique, condition, age and mentality; (2) the surgeon's requirements; and (3) the length and nature of the operation. If the anæsthesia requires to be prolonged, a combination of nitrous oxide, chloroform and ether, or alcohol, chloroform and ether may be selected. In cases where the heart is weak, or otherwise diseased, ether should be preferred and chloroform avoided. But if damage to the heart is great, ether should also be avoided as being dangerous on account of the strain on the damaged heart during excitement. Active bronchitis or indeed a moist chest of any sort should preclude the use of ether. Children are specially susceptible to ether irritation and it is not suitable for operations about the mouth and larynx. Sometimes a few whiffs of nitrous oxide gas makes ether more pleasant.

Within recent years alkaloidal narcotics have been used with volatile anæsthetics, with the idea of producing complete anæsthesia without giving ether in high concentrations. With this idea hyoscine hydrobromide $\frac{1}{100}$ gr. or atropine sulphate $\frac{1}{100}$ to $\frac{1}{80}$ gr. and morphine hydrochloride $\frac{1}{2}$ gr. is administered an hour before the anæsthetic is given. This combination reduces the concentration of ether necessary to produce anæsthesia and atropine will diminish the secretion of mucus so frequently seen with ether. Atropine is preferred to hyoscine as it does not depress the respiratory centre and also prevents reflex vagus inhibition of the heart.

The differences between chloroform and ether are tabulated below:—

Ether	Chloroform
1. Ether is a weaker anæsthetic and should be used in a concentrated form : 6 p.c. by volume or 15 p.c. by weight	Chloroform must be given well diluted; 97 to 98 p.c. of air and 2 to 3 p.c. of chloroform.
2. Ether being inflammable, no fire should be brought close to the mouth.	Chloroform is not inflammable.
3. A large quantity (several ounces) is needed to produce anæsthesia.	A small quantity, 3 drs. to 1 oz. is enough.
4. The smell of ether is disagreeable.	The smell of chloroform is not disagreeable.
5. The stage of stimulation is very much protracted and there is more struggling.	The stage of stimulation is shorter, and therefore less struggling.
6. The stage of anæsthesia is shorter, and the degree of anæsthesia is less profound.	The stage of anæsthesia is more complete, and the degree more profound.
7. The fall of temperature is great (Hare observed 4.4°F. in man).	The fall of temperature is slight.
8. Nausea and vomiting common after-effects.	Nausea and vomiting less common after-effects.

Ether

9. Muscular relaxation not so easily produced.

10. Not toxic to liver and kidneys.

11. Cardiac, respiratory, and vaso-motor centres are not readily paralysed; hence ether is a *safer* anæsthetic.

12. Bronchial and lung complications such as bronchitis, pneumonia are frequent.

13. Elimination is slow, and the smell hangs about the body for a long period.

14. Death from syncope during inhalation is less probable in subjects of cardiac weakness.

Chloroform

Muscular relaxation easily produced.

Toxic to liver and kidneys.

Cardiac, respiratory and vaso-motor centres are readily paralysed, hence chloroform is *not* so safe an anæsthetic.

Bronchial and lung complications are uncommon.

Elimination is rapid, and the smell does not hang about so long.

Death from syncope is more probable in subjects of cardiac weakness.

Preliminary basal anæsthesia.—The expression indicates a state of unconsciousness produced by a non-volatile substance which serves as a base upon which complete anæsthesia can be built up by the administration of a volatile anæsthetic. Recently attempts are being made to use some non-volatile narcotics as adjuvant drugs before the administration of the anæsthetic proper, with the object of protecting the nervous system by producing profound sleep, thus making the patient indifferent to subsequent happenings. In fact this method, which is known as **basal narcosis**, is receiving considerable importance, inasmuch as more reliance is being placed on these preliminary measures than on the subsequent anæsthetic. It obviates all nervous apprehensions and mental distress so often responsible for true shock. Moreover with the introduction of these preliminary anæsthetics the use of chloroform has been much curtailed, and the necessity of using large amounts of ether considerably reduced. The drugs used for the purpose are morphine, hyoscine hydrobromide, avertin, paraldehyde, amytal, nembutal, luminal, evipan and pernocton. These will be considered under their respective heads.

VENYL ETHER. *Syn.*—*Vinesthene*—A volatile, clear, colourless liquid with a peculiar odour. It is a powerful anæsthetic, its potency being four times that of ether, and is inflammable. Anæsthesia is produced very quickly, within $\frac{1}{2}$ to 1 minute with little excitement. Any degree of muscular relaxation can be obtained with it. Recovery is very rapid. The relative safety of this anæsthetic over ether is still unsettled, and cases are on record where it produced damage to the liver. Owing to the rapid action, ease of administration and comparative safety to the mother and the child it is suitable in obstetric practice. Best administered by the closed method with oxygen, although open drop method can be used for short period, not longer than one hour.

Anæsthetic Gases**AETYLENUM**

Ethylene. (*Æthylen.*) C_2H_4

Syn.—Olefiant Gas.

Source.—May be obtained from the products of decomposition of petroleum. Contains not less than 98 p.c. v/v of ethylene. It may be compressed in metal cylinders.

Characters.—A colourless, inflammable gas, with a slightly sweet odour and taste. One volume dissolves in 9.2 volumes of water, in about half a volume of alcohol (95 p.c.) at $25^\circ C.$, and in about 0.05 volume of ether at $15.5^\circ C.$

PHARMACOLOGY AND THERAPEUTICS

At ordinary temperature and pressure ethylene exists as a gas and induces *general anaesthesia* when inhaled with oxygen. The effects are similar to those of ether which it resembles, but more rapid in onset, in which respect it resembles nitrous oxide gas. Its effects are stronger than nitrous oxide, and the anaesthesia is sufficiently deep to be employed for operations requiring muscular relaxation.

The gas as obtained in compressed cylinders has a garlic smell and although the patient does not perceive it for more than a few breaths, it is annoying to the anaesthetist and other occupants of the room.

The usual practice is to give 90 p.c. of the gas with 10 p.c. of oxygen. For prolonged use it should be more freely diluted with 20 p.c. oxygen. As a rule the period of excitement is absent or relatively slight and the respiration is not affected, but remains slow and regular. The medullary centres are stimulated slightly by the lowered oxygen concentration. The skin remains dry and there is no perceptible increase either of perspiration or of salivary secretion. Post anaesthetic vomiting and "gas pains" are rare, and less common than with ether.

Recovery takes place quickly, within two to three minutes, after withdrawal of the anaesthetic.

It is used in the same way and with the same apparatus as nitrous oxide; it is however safer, asphyxia or cyanosis being absent. As compared to nitrous oxide gas it produces complete muscular relaxation and deeper anaesthesia. Moreover excitement is less and recovery is more quick.

It differs from ether in being more pleasant, prompt and safe. There is absence of gas pains and vomiting, renal and pulmonary complications.

Caution.—The gas is inflammable and when mixed in certain proportions with air or oxygen it becomes explosive. It should not be used where open flame or cautery is used.

CYCLOPROPANE. *Syn.*—*Trimethylene.*—It is a gas and an isomer of propylene, heavier than air and inflammable, and will cause explosion in concentrations of 20 to 75 p.c. when mixed with oxygen. It is a powerful anaesthetic and will produce narcosis in low concentrations (4 p.c.) and may be used mixed with air. It is a safe, pleasant, non-irritating, non-toxic anaesthetic producing relaxation of the muscles. The anaesthesia can be maintained for several hours if required but the relaxation of the muscles is not easily obtained. The gas is administered in closed apparatus with carbon dioxide absorption technique with oxygen.

Disadvantages.—Possibility of explosion; increased hæmorrhage from raised blood pressure (capillary bleeding); tendency to respiratory depression or even arrest during deep anaesthesia; cost.

Advantages.—High percentage of oxygen compatible with full anaesthesia without premedication, and absence of irritation of respiratory passages. Suitable for major thoracic surgery and bad

risk cardiac cases, e.g. total thyroidectomy for congestive heart failure.

NIT GENII ONOXI U

Nitrous Oxide. (Nitrogen. Monox.). N_2O

Syn.—Laughing Gas.

Source.—Prepared by heating ammonium nitrate. Supplied compressed in metal cylinders. Contains not less than 93 p. c. v/v of nitrous oxide.

Characters.—A colourless gas, heavier than air, with a characteristic odour and faint sweetish taste.

PHARMACOLOGY AND THERAPEUTICS

Nitrous oxide is a gas and produces general anæsthesia almost instantaneously, partly by direct narcotic action on the central nervous system and partly by exclusion of oxygen and inducing anæsthesia. Its action on the central nervous system is possibly due to its solubility in lipoids. The mixture used contains 20 p.c. of air and so 4 p.c. of oxygen, therefore the inhalation cannot be continued for more than a few minutes. Nevertheless it produces sufficient anæsthesia to enable the surgeon to perform small operations, like extraction of tooth or incision of an abscess, painlessly.

The anæsthesia is brought about so quickly that the different stages can hardly be differentiated. At the beginning there is some buzzing of the ear and indistinctness of vision, soon followed by impairment of consciousness, a pleasurable sensation, and a tendency to laugh (hence the name laughing gas). As soon as the inhalation is stopped the patient returns to consciousness, and the cyanosis disappears within half to quarter of a minute. The pulse becomes slower and fuller, and the respiration returns to normal.

For prolonged anæsthesia the gas is used with oxygen, or given after a preliminary dose of morphine and hyoscine, as then the anæsthesia can be produced without the risk of asphyxia. When given with oxygen there is less disturbance of the vital centres than with any other general anæsthetic. Moreover the anæsthesia can be prolonged without any fall of blood-pressure, depression of respiration or post-operative shock.

It is impossible to obtain with nitrous oxide and oxygen alone sufficient muscular relaxation, because at the ordinary atmospheric pressure the blood cannot take up sufficient nitrous oxide to produce deep anæsthesia. If, however, it is used with small quantities of ether, a relaxation of the muscle is obtained which is out of proportion to the amount of ether used, and this becomes more marked when ether and chloroform are used in combination. To secure better control of the proportion of gas and oxygen various forms of apparatus have been devised. For small operations it is administered through a tight-fitting mask to exclude air.

Gas and oxygen is the ideal anæsthetic because of its

nearest approach to 100 p.c. safety. Unfortunately the apparatus is expensive and bulky and is liable to mechanical breakdown and requires constant and careful looking after to keep it in working order.

For satisfactory surgical anæsthesia 94 to 96 p.c. of N_2O is needed thus a certain amount of anæsthesia is always present.

As a rule no after effects are observed, and it is practically devoid of any danger except asphyxia from want of oxygen which may cause a rise of blood pressure to a dangerous extent in elderly persons. Some complain of giddiness, headache and drowsiness.

Contra-indications.—Elderly persons with arterio-sclerosis, those suffering from valvular and myocardial disease, obese and anæmic persons, and in operations on the brain.

AET HYL CHLORIDE

Ethyl Chloride. (Æthyl. Chlor.). C_2H_5Cl

Source.—Obtained by the action of hydrogen chloride on ethyl alcohol, or on Industrial Methylated Spirit.

Characters.—Gaseous at ordinary temperatures and pressures, but as usually supplied is condensed into colourless, mobile, inflammable, and very volatile liquid. *Odour*, pleasant and ethereal. Slightly soluble in water, miscible with alcohol (90 p.c.), and ether.

PHARMACOLOGY AND THERAPEUTICS

Ethyl chloride is both a local and general anæsthetic, and being extremely volatile is largely used in the form of spray to produce local anæsthesia in dental practice and minor surgery. As this anæsthesia does not penetrate into the deeper tissue it cannot be used for deep surgical operations. When inhaled it resembles chloroform in its action and depresses the heart like chloroform, though less powerfully. Consequently the blood-pressure falls, due partly to the depressed action of the heart and to the relaxation of the blood-vessels. Being very volatile it is administered in a concentrated form, for this purpose a mask similar to that used for nitrous oxide gas may be used. An ordinary glass funnel with some loose absorbent cotton-wool serves the purpose equally well; the broad end being placed over the mouth, ethyl chloride is sprayed upon the cotton through the small end. It should be remembered that excepting in children, corneal reflex is not lost in ethyl chloride anæsthesia, and that it is not of much value when muscular relaxation is required. Ethyl chloride is a comparatively safe anæsthetic and may be used to produce primary anæsthesia before administration of ether or chloroform. It is contra-indicated in serious diseases of the heart and myocardial degeneration, where ether is safer.

3. HYPNOTICS

Hypnotics are drugs or measures employed to induce or maintain sleep. Sleep is a natural phenomenon which comes on spontaneously

when the reflex activity of the central nervous system is inhibited to a degree which is usually accompanied by unconsciousness. The unconsciousness is not deep, as in coma, but more or less shallow. Like most habits, sleep is to a certain extent under voluntary control and is a natural sequence which follows after a period of wakefulness. Prolonged sleeplessness is accompanied by various pathological changes in the cerebral cortex and the appearance of some toxin in the blood.

A proper use of hypnotics implies a knowledge of the mechanism of sleep and the different factors concerned in producing sleeplessness or insomnia. As long as the mechanism of sleep remains in part unexplained the treatment of insomnia must at best be empirical. Sampson Wright has put forward the theory that it may be due to the damping down of the conductivity in the afferent and association paths in the nervous system. Although such a conception does not explain all the factors concerned in sleep, it acts as a reminder to the physician of the existence of the paths through which sleeplessness may come. Besides there are extro-ceptive impulses from the external surroundings of the patient through the surface of the body and special senses; the proprio-ceptive impulses from the posture of or pressure on the muscles, bones, joints, and from the large group of visceral stimuli, of which the cardio-vascular, gastric and rectal are the most important.* The fact remains however that accompanying sleep there is a depressed activity of the cerebral cortex, and that any factor, physical or mental, which tend to perpetuate cortical activity—pain and dyspnoea, worry and strain—render sleep more difficult.

Whatever may be the underlying factors in the production of natural sleep, it is evident that in the majority of cases of insomnia the cause is the presence of some factors inimical to that state of physical or mental equanimity so essential to natural sleep, and the rational course of treatment would be to remove the disturbing factor.

The following factors are mostly responsible for sleeplessness :—

1. *Obstructive*.—1. *Pain*, from whatever cause it may arise, and the proper treatment is to allay the pain either by dealing directly with the primary disease responsible for it, or to make the patient forget its presence by the use of such drugs as morphine or any of its allies, barbiturates or other analgesics according to the intensity of the case.

2. *Certain general and visceral diseases*.—Diseases of the heart, vessels, kidneys, etc., often cause sleeplessness. Cough and dyspnoea are often responsible for sleeplessness. Cough may be a part of serious lung complication, or due to some local trouble in the throat. The rational treatment is to remove the disturbing factor, whenever possible, supplemented by the use of proper hypnotic drugs. Digitalis will often induce sleep in dyspnoea from failure of the heart.

3. *Intoxications*.—Excessive tea and coffee drinking often cause insomnia. With some people a cup of tea or coffee before bedtime will cause sleeplessness.

4. *Infectious Diseases*, when accompanied by high fever, e.g. malaria, pneumonia, etc.

5. *Diseases of the Brain*—(a) Organic, as tumour, meningitis, syphilis; and (b) mental, as mania, delirium tremens, etc.

II *Psychoneurosis*—By far the largest number of insomnia comes under this head which plays an important part in the mental and emotional excitement. These may be worry, grief, neurasthenia, hysteria, hypochondria, etc. A state of anxiety or preoccupation is a common factor in the production of insomnia, for instance the dread of not being able to sleep, active mental work, exciting companions, disturbing surroundings, etc., before sleep. Often times the patient

* *Practitioner*, Feb 1938 Ibid Sept. 1936.

goes to bed with his mind fixed on the necessity of sleep—a state specially liable to perpetuate sleeplessness.

According to Verworn sleep is due to (1) lessened irritability, *i.e.* fatigue of the cells of the cerebral cortex which results from work; (2) removal of external stimuli, as noise, light, etc. A sound which is of a monotonous nature, *e.g.* continuous falling of rain, or a mild form of peripheral stimulus, which will not excite any emotion, will have a soothing effect on the brain cells conducive to sleep. Many cases of insomnia due to psychoneurosis yield to suggestion. If the patient knows that he will get something for sleep, the knowledge will of itself bring on sleep. At the same time if he knows that the drug is to be discontinued or the dose reduced, the dread of a sleepless night will cause insomnia. Similarly if an injection of, say morphine is given to produce sleep, oftentimes an injection of some inert substance, even water, will have the same mental effect to produce sleep. The effect of monotonous sound, monotonous thought and monotonous sight in the production of sleep is well depicted by Wordsworth.*

The different hypnotics vary in their speed of action, duration of their effect and suitability for various ages and physical states. It is useless for instance to order a hypnotic when the patient is up and about, or to prescribe paraldehyde to a patient who goes to sleep in time but wakes up after 3 to 4 hours.

The action of hypnotics resembles somewhat that of general anæsthetics, but is slower in its onset, less powerful, more lasting and is not intended to produce a deep stage of narcosis. An ideal hypnotic must not irritate the stomach and should be absorbed readily, so that sleep may be induced at a regular interval after its administration and without producing any preliminary excitement. It should not be volatile and must not be excreted too rapidly by the lungs. It should not produce any narcotic effect, *i.e.* should not depress the cerebrum more than the sleep stage, and should have no untoward effect either on the vital medullary centres, or the heart. There must be a sufficient margin of safety between the therapeutic and toxic doses. Moreover it should not have any toxic effect even when used for a prolonged period and should not form a habit. Such an ideal hypnotic is not known at present.

Of the different hypnotics, chloral, bromides, paraldehyde, avertin act by depressing the cerebral cortex; while the barbituric acid group act by depressing the thalamic region. The barbiturates therefore, in addition to the hypnotic effect, are markedly sedative and are of great service in conditions characterised by motor hyperexcitability. Morphine and hyoscine are supposed to act on both the regions.

Hypnotics may be classified as follows:—

A. Organic

1. Alkaloidal Hypnotics

Opium, Morphine, Codeine, Apomorphine, Hyoscine

Opium, Morphine and its derivatives produce sleep and relieve excessive pain

2 Aliphatic Hypnotics

(a) Chloral Group Chloral Hydrate, Butyl-chloral Hydrate, Chlorbutol, Chloral formamide

* "A flock of sheep that leisurely pass by,
One after one, the sound of rain, and bees
Murmuring the fall of rivers, wind and
seas,

Smooth fields, white sheets of water, and
pure sky.

I have thought of all by turns, and yet do lie
Sleepless!"

- (b) Aldehyde and Alcohol Group **Paraldehyde, Avertin**
 (c) Sulphonal Group **Sulphonal, Methylsulphonal, Ethylsulphonal**
 (d) Urea Derivatives **Barbitone, Soluble Barbitone, Phenobarbitone, Soluble Phenobarbitone, Carbromal, Bromural, Amytal, Sodium Amytal, Pentobarbital Sodium, Evipan, Evipan Sodium, Urethane**

Paraldehyde, Avertin and some of the barbiturates are also used as sedatives and anæsthetics

3. Aromatic Hypnotics

(a) Alkaloidal Hypnotics: See above

(b) Phenacetin, Acetanilide, Amidopyrine, Phenazone, Acid Acetylsalicylic These are not true hypnotics but often produce sleep by relieving neuralgic pain through their analgesic action.

B. Inorganic: Potassium Bromide, Sodium Bromide, Ammonium Bromide

These diminish hypersensibility of the nervous system so that pain is less keenly felt.

1. Alkaloidal Hypnotics

PIU

Opium. N.O. *Papaveraceæ*

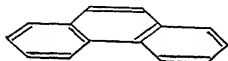
Syn. I.V.—*Afim*, Beng., Hind. *Akfen*, Sans.

Source.—Obtained by incision from the unripe capsules of *Papaver somniferum*, and inspissated by spontaneous evaporation. It contains in its moist condition, not less than 9.5 p.c. of morphine.

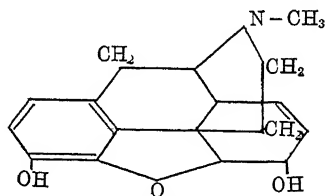
Characters.—More or less rounded, usually somewhat flattened masses, varying in weight, from 250 and 1000 grammes; covered with portions of poppy leaves, and usually with fruits of species of *Rumex* adhering to the masses. When fresh, plastic, becomes hard and tough on keeping, or brittle. Odour, strong and characteristic. Taste, bitter.

Varieties.—(a) *Turkey opium*, produced in Asia Minor, in rounded, irregular, or flattened masses, usually enveloped in poppy leaves or fruits of a species of *Rumex* to prevent the masses from adhering to one another. Two varieties, viz. "Soft Shipping," which may contain up to 30 p.c. of moisture, and the "Druggists opium" which contains less moisture and less per cent. morphine. (b) *European opium*, chiefly produced in Belgium, Greece and Yugoslavia, is of a higher quality than the "Soft Shipping" variety of Turkey opium which it resembles in general characters. (c) *Persian opium*, in brick shaped masses weighing about 1 lb. usually wrapped in red paper tied with red or yellow string; it contains less moisture, is homogeneous in character, and usually contains varying proportions of native gum to give the consistence suitable for moulding them into bricks. (d) *Indian opium*, occurs in two forms, viz. *Abkari* or *excise opium* in square cakes covered with Nepal paper; *Medicinal opium*, in cakes and powder.

Composition.—The important alkaloids belong to two groups. (1) *Phenanthrene alkaloids*, viz. morphine, codeine and thebaine; and (2) *Isoquinoline alkaloids*, viz. narcotine, papaverine, laudanosine, narceine, hydrocotarnine, etc.



Phenanthrene nucleus



Morphine

(1) *Primary alkaloids* 18 in number which form a closely related series at one end of which stands *morphine*, with its dominant property, the narcotic one, and at the other end *thebaine* with a typical strychnine action on the cord. On account of these other substances opium is less narcotic than morphine:—

<i>Morphine</i> up to about 5 to 21 p.c.	Pseudo-morphine	Meconidine
<i>Codeine</i> about 0.3 to 4 p.c.	Cryptopine	Rhœadine
<i>Thebaine</i> about 0.3 p.c.	Protopine	Codamine
Anarcotine or <i>Narcotine</i> , 2 to 7 p.c.	Hydrocotarnine	Gnoscopine
Narceine	Laudanine	Lanthopine
Papaverine	Laudanosine	Xanthaline

(2) *Secondary Alkaloids or Derivatives*, 8 in number:—

Apomorphine	Apocodeine	Thebenine	Cotarnine
Oxydimorphine	Desoxycodine	Porphyroxine	Rhœadenine

(3) *Indifferent Substances*, 3 in number:—

Opionin	Meconin	Meconoidin
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(4) *Organic Acids*, 2 in number:—Lactic acid, Meconic acid

(5) *Water*.—About 16 p.c.

(6) Resin, glucose, fats, caoutchouc, essential oil, odorous substances and salts of ammonium, calcium, and magnesium.

Variation in composition.—The percentage of morphine varies in Patna opium from 3 to 5, and in Smyrna opium from 5 to 10½, whereas that of narcotine in the former 4 to 6 and in the latter 1 to 2.

Incompatibles.—Tannic acid and astringent vegetable preparations, salts of zinc, copper, iron, arsenic, lead and silver. Alkalies, their carbonates, and ammonia.

✓ PIU ULVE ATU

✓ Powdered Opium. (Opium Pulverat.)

Syn.—*Pulvis Opii*.

Source.—Opium dried at a moderate temperature, reduced to a fine or moderately fine powder, and adjusted if necessary, by the addition of powdered lactose to contain 10 p.c. of morphine, or $\frac{2}{17}$ gr. morphine in 3 grs.

Characters.—A light brown powder, consisting of yellowish-brown or brownish-red particles; odour and taste, of opium.

B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm.

OFFICIAL PREPARATIONS

1. *Extractum Opii Siccum*.—Contains 20 p.c. of morphine, or $\frac{1}{3}$ gr. in 1 gr. B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.

2. *Pulvis Cretæ Aromaticus cum Opio*.—Contains 2.5 p.c. of opium, or 0.25 p.c. of morphine; or $\frac{1}{4}$ gr. morphine in 60 grs. B.P. Dose.—10 to 60 grs. or 0.6 to 4 grm.

(3) *Pulvis Ipecacuanhæ et Opii*. Syn.—*Pulv. Ipecacuanhæ Co.; Dover's Powder*.—10 p.c. of opium, or 1 p.c. morphine; or $\frac{1}{17}$ gr. morphine in 10 grs. B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

4. *Suppositorium Plumbi cum Opio*.—Lead acetate 3 grs. and powdered opium 1 gr. in each.

5. *Tinctura Opii*. Syn.—*Laudanum*.—Contains 1 p.c. morphine, or $\frac{1}{4}$ gr. in 30 ms. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.

6. *Tinctura Opii Camphorata*. Syn.—*Tinct. Camphoræ Co., Paregoric; Paregoric Elixir*.—0.05 p.c. w/v morphine, or $\frac{1}{37}$ gr. in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

NON-OFFICIAL PREPARATIONS

1. *Pilula Plumbi cum Opio*, B.P.C.—Lead acetate $\frac{1}{16}$ grs and opium about $\frac{1}{4}$ gr. for each pill with syrup of glucose Dose.—1 to 2 pills.

2. *Pulvis Kino Co*—Kino 75, opium 5, cinnamon 20 5 p.c. opium *Dose*—5 to 20 grs or 0.3 to 1.2 grm
3. *Unguentum Gallæ cum Opio*.—Ointment of gall and opium. Opium $7\frac{1}{2}$ p.c.
4. *Nepenthe* *Syn*—*Anodyne Tincture*.—Similar to, and is given in same dose as, *Tinctura Opii*. Contains 0.84 p.c. morphine
5. *Liquor Opii Sedativus B.P.C.*—Contains 0.95 to 1.05 p.c. w/v morphine. *Dose*—5 to 30 ms. or 0.3 to 2 mil
6. *Pilulæ Hydrargyri c. Creta et Opii* *Syn*.—*Hutchinson's Pills*—Grey powder and Dover's powder, each 1 gr. for each pill *Dose*—One pill.
7. *Narcotina* *Syn*.—*Anarcotine*.—White odorous crystalline prisms Insoluble in water. It is not a hypnotic but is an antiperiodic, in which respect it resembles quinine *Dose*—1 to 3 grs or 0.06 to 0.2 grm
8. *Cotarnine Chloride*, B.P.C *Syn*—*Stypticin*.—The chloride of an alkaloid prepared from narcotine. Yellow crystalline powder, very soluble in water and alcohol. Useful in *uterine hæmorrhage*, and to check bleeding from the urethra after catheterisation. *Dose*— $\frac{1}{3}$ to $1\frac{1}{2}$ grs. or 0.02 to 0.1 grm.
9. *Papaveretum* *Syn*.—*Omnapon*, *Pantopon*.—Consists of the hydrochlorides of alkaloids of opium. Contains 47.5 to 52.5 p.c. morphine. Soluble brown powder. Used for the same purposes as opium. Usually used hypodermically. A 2 p.c. solution in a mixture of 3 parts of water and 1 part of glycerin is suitable for internal administration or hypodermic use. The preparations for injection may be sterilised by heating. *Dose*— $\frac{1}{12}$ to $\frac{1}{6}$ gr. or 0.01 to 0.02 grm by mouth; $\frac{1}{12}$ to $\frac{1}{6}$ gr or 0.005 to 0.01 grm by injection

M O R P H I N E H Y D R O C H L O R I D E

(Morph. Hydrochlor.)

✓ *Morphine Hydrochloride*. $C_{17}H_{19}O_3N, HCl, 3H_2O$

Source.—Hydrochloride of an alkaloid, morphine, obtained from opium.

Characters.—Colourless, glistening needles or crystalline powder; odourless; taste, bitter. *Soluble* in 25 parts of water, 50 parts of alcohol (90 p.c.), insoluble in ether and chloroform. Aqueous solution neutral to litmus.

B.P. Dose.— $\frac{1}{3}$ to $\frac{1}{2}$ gr. or 0.008 to 0.02 grm.

OFFICIAL PREPARATIONS

1. *Liquor Morphinae Hydrochloridi*.—Contains 1 p.c. w/v of morphine hydrochloride, or $\frac{1}{4}$ gr. in 30 ms. *B.P. Dose*.—5 to 30 ms. or 0.3 to 2 mils.
2. *Suppositorium Morphinae*.—Contains $\frac{1}{4}$ gr. morphine in each.
3. *Trochiscus Morphinae et Ipecacuanhæ*.— $\frac{1}{32}$ gr. morphine and $\frac{1}{16}$ gr. ipecacuanha in each.

NON-OFFICIAL PREPARATIONS

1. *Linctus Morphine*, U.C.H.—Liq Morph Hyd 3 ms, Chloroform emulsion 3 ms., Treacle 60 grs., Water to 1 dr. *Dose*—1 dr. 3 or 4 times or oftener daily. Children of 8 to 14 years, 10 to 20 drops.
2. *Tinctura Chloroformi et Morphinae Composita*.—Chloroform $\frac{3}{4}$ m, Acid. Hydrocyanicum Dil $\frac{1}{2}$ m, and Morphine Hydrochlor $\frac{1}{12}$ gr in 10 ms. *Dose*.—5 to 15 ms or 0.3 to 1 mil

M O R P H I N E T A R T R A T E

(Morph. Tart.)

✓ *Morphine Tartrate*. $(C_{17}H_{19}NO_3)_2, C_4H_6O_6, 3H_2O$

Source.—A tartrate of an alkaloid, morphine, obtained from opium.

Characters.—Minute, acicular, colourless crystals; odourless; taste, bitter. Effloresces on exposure to air. *Soluble* in 11 parts of

water, sparingly in alcohol (90 p.c.), almost insoluble in ether and chloroform. Aqueous solution neutral to litmus

B.P. Dose.— $\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0.008 to 0.02 grm.

ADDITIONAL NON-OFFICIAL PREPARATIONS

1 **Morphinæ Acetas.**—A white crystalline or amorphous powder. Soluble 1 in $2\frac{1}{2}$ of water, about 1 in 100 of alcohol (90 p.c.), and 1 in 5 of glycerin
Dose— $\frac{1}{8}$ to $\frac{1}{4}$ gr or 0.008 to 0.02 grm

2 **Morphinæ Sulphas, U.S.P.**—Colourless acicular crystals. *Solubility*—1 gm in 15.5 c.c. of water, freely in hot water Dose U.S.P.— $\frac{1}{8}$ gr or 0.008 grm

3 **Dionin Syn.—Ethyl-Morphine Hydrochloride, U.S.P.**—A white or yellowish crystalline powder, soluble in water Pleasant substitute for morphine without its undesirable effects Recommended in morphine habit It has properties intermediate between morphine and codeine, but does not depress respiration to the same extent as morphine. Relieves dry *hacking cough* Useful in *bronchitis and whooping cough* A useful anodyne in *glaucoma,ritis, corneal ulcers*, etc., when used locally. Dose U.S.P.— $\frac{1}{4}$ gr or 0.015 grm

4 **Papaverine Sulphate.**—A white crystalline soluble salt *Antispasmodic* in intestinal, biliary and renal colics and bronchial asthma Useful in *vomiting* of pregnancy and after *anæsthesia*. It has no action on the heart In *angina pectoris*. Dose.—2 to 4 grs or 0.12 to 0.25 grm by mouth or hypodermically

5. **Dilaudid—Hydrochloride of dihydromorphine**—Colourless, bitter crystals, freely soluble in alcohol and water $\frac{1}{32}$ gr. is equivalent to $\frac{1}{8}$ gr morphine as an analgesic Used with benefit in *pleurisy, sciatica, facial neuralgia*, and *acute arthritis* in place of morphine Affects respiratory centre like morphine Does not cause severe constipation and is less liable to form habit. May cause transient nausea and giddiness Dose— $\frac{1}{60}$ to $\frac{1}{32}$ gr. or 0.0012 to 0.0025 grm by mouth, $\frac{1}{32}$ gr or 0.002 grm subcutaneously.

6 **Eukodal—Hydrochloride of dihydroxycodemeone** Prepared from thebaine White crystalline powder, soluble in water. Not so toxic as dilaudid or dicodid and does not cause convulsion. It has much weaker action on the intestinal movements than the other two It is more depressant to the respiratory centre than morphine A substitute for morphine as an analgesic and sedative Depresses the vagal centre Used in all cases where morphine is indicated Does not produce vomiting or constipation Though prepared from non-habit forming drug it is liable to produce a habit Dose—As analgesic, $\frac{1}{32}$ to $\frac{1}{8}$ gr. 0.005 to 0.01 grm or 1 to 2 tablets $\frac{1}{8}$ to $\frac{1}{4}$ gr (0.01 to 0.02 grm) subcutaneously.

PHARMACOLOGY OF OPIUM AND MORPHINE

Externally.—Opium and its alkaloids have no action on the sensory nerve endings or on the peripheral nerves. As morphine is absorbed to a slight extent from the unbroken skin and freely from the mucous membrane there may be some central analgesia.

Internally. Mouth and stomach.—In moderate doses opium causes dryness of the mouth, tongue and throat from diminished secretion due to its depressant action on the secretory centre of the salivary and the mucus glands. In the stomach small doses ($\frac{1}{12}$ gr.) diminish the sensation of hunger and slightly increase its movements; but larger doses cause contraction of the pyloric sphincter and relaxation of the fundus, and retards the passage of its contents by several hours. The gastric movements are diminished and the secretion is reduced, though it is subsequently increased. Opium therefore relieves pain, lessens appetite

and retards digestion. These effects are central and observed after the drug is absorbed. It often causes nausea and vomiting which are not due to irritation of the gastric nerves, since they are not so marked in the early stage, but occurs during recovery from its effects and even when used subcutaneously. It is possibly due to the formation of some compound with an apomorphine like effect on the centre. The centre is subsequently depressed, and in poisoning afferent impressions or direct emetics do not induce vomiting.

Intestine—In the intestine opium **reduces secretion, relieves pain and produces constipation**. The cause of constipation has been the subject of much controversy and has been differently explained by different observers. While some demonstrated diminished peristalsis, others claimed marked stimulation. Apart from individual variations, it is possible that the presence of other alkaloids, specially papaverine and narcotine, which have a strong depressant action on peristalsis, may be responsible for the difference in the effects produced. All recent observations however tend to indicate that with morphine the tone and peristaltic activity of the duodenum, jejunum and ileum are increased, while in the case of the colon may take the form of spastic contraction. These effects suppress the normal peristaltic waves and retard the passage of the contents downwards. The spasm of the ileo-cæcal and anal sphincters together with the tonic contraction of the pyloric sphincter, already referred to, allow the food materials to remain for a longer time, thus helping more complete absorption of fluids and accumulation of inspissated fæcal mass. Moreover owing to the central effect, the rectal sensation is diminished and the defæcation reflex becomes sluggish. Opium therefore is a **sedative, astringent and anodyne** to the bowels. It also relieves, through central effect, pain and irregular peristalsis thus relieving colic. In intestinal colic, therefore, opium by relieving spasm may cause evacuation of the bowels. The secretion of pancreas is diminished by its direct action on the gland.

To sum up the different factors concerned in producing constipation :—(1) delay in emptying the stomach owing to pyloric spasm and relaxation of the stomach wall ; (2) diminished reflex peristalsis owing to loss of sensation ; (3) spasm of ileo-cæcal and anal sphincters ; (4) spastic contraction of the colon ; (5) diminished secretion ; and (6) sluggish rectal sensation and defæcation reflex.

If a large dose is introduced directly into the circulation of animals like cat or dog, it causes vomiting and purging through increased tonus and peristalsis of the muscles of the intestine. No such effect is however observed in man even in poisoning or when a large dose of morphine is given

as injection, except vomiting. It has been suggested that the action of morphine depends on two factors, one when the drug is in the blood and the other when excreted into the gut. Augmented peristalsis occurs during the time the drug is in circulation and is due to a depressant effect on the sympathetic ganglia, splanchnic being the inhibitory nerve to the intestine. When the drug is excreted into the intestine the effect is opposite to augmented peristalsis and it is for this effect that opium is extensively used and is due to some effect on the peripheral nervous mechanism. It should be noted that opium is superior to morphine in relieving intestinal pain and producing constipation, due firstly to its slow absorption, and secondly to the presence of isoquinoline derivatives, *viz.* papaverine and narcotine which induce relaxation of the plain muscles.

Liver.—Biliary secretion is considerably reduced, causing the stools to be pale or clay-coloured, or jaundice may set in. Butsch, McGowan, and Walters, of the Mayo Clinic.* have studied the effect of intrabiliary pressure in the causation of pain and the effect of morphine in patients after cholecystectomy. It was observed that after an injection of morphine ($\frac{1}{2}$ gr.) the pressure rose from a normal of 0 20 mm. to 200 to 300 mm. of water, and during this rise there was epigastric pain and discomfort resembling biliary colic which disappeared slowly with the effect of morphine on the central nervous system. These observers maintain that the increased pressure was due to increased tone and spasm of the sphincter of the common bile duct. These effects are relieved by the administration of amyl nitrite or nitroglycerin but not of atropine.

Heart and circulation.—Morphine is rapidly absorbed from all mucous surfaces and soon disappears from the blood being partly fixed in the organs but largely destroyed, so that only a small fraction can be recovered in the autopsy. In therapeutic doses it has very little effect on the heart except that it is slowed from stimulation of the vagal centre, and slightly strengthened in force. This effect is antagonised by atropine. The cardiac muscles are only indirectly affected by large doses through low blood-pressure and asphyxia. But the circulation remains fairly good till the last; in fact death in opium poisoning is *not due to the failure of the heart, but to the paralysis of the respiratory centre*, as will be seen presently. The blood-pressure is not influenced in therapeutic doses, although there is flushing of the face and dilatation of the skin vessels. In toxic doses blood-pressure falls due to vaso-motor depression. During asphyxia the face becomes cyanotic and of purple colour due to the vessels remaining dilated. As asphyxia advances

* *Jour. Amer. Med. Assoc.*, 1936.

the pulse may become slow, while the blood-pressure varies depending upon the vaso-motor centre and the heart. Since these effects can be abolished by aerating the blood sufficiently by artificial respiration these effects are indirect through the respiratory centre.

Respiration.—In small non-narcotic doses morphine will quiet the respiration, making it slow specially if it was quick and increase its depth if it was shallow. The rate becomes progressively slower and in larger doses it causes **depression of respiration**. In poisoning the respiration becomes very slow, even down to three or four per minute. The individual respirations eventually become shallow and irregular and before death assumes Cheyne-Stokes type. According to Barbour this results from depression of the centre and consequent asphyxia of the heart which leads to variation of the blood-pressure and blood supply to the brain. During natural sleep and also in sleep following a hypnotic the breathing becomes slow because less oxygen is required for the inactive body, but the CO_2 content of the blood remains unchanged. In morphine poisoning the CO_2 content of the blood is increased and in large doses the respiratory centre loses its sensitiveness, and greater than normal percentage of CO_2 is required to bring about respiration. Morphine and its derivatives depress the excitability of the **respiratory centre**. Death takes place from paralysis of the centre and asphyxia. The cough centre is also depressed, in fact morphine, dionin and codeine reduce the sensibility of the cough centre in very small doses.

Bronchial muscles are slightly relaxed by therapeutic doses of morphine, but more powerfully by papaverine and narcotine. This relaxation is of value in giving relief in bronchial spasm. It is well to remember that the bronchial muscles are contracted in toxic doses. Unless there is nausea, the secretion of mucus is diminished, possibly due to suppression of cough and longer stay of the mucus in the bronchi, and consequent absorption of the water.

Nervous system.—The chief action of opium is on the nervous system. In small doses, it first excites the **higher faculties**. During this stage, with a few the excitement is a pure exaltation of feelings, the imagination being pleasantly excited with a sense of happiness and comfort and the animal tendencies are set free. With others, the intellectual activity is heightened, and they can concentrate their energies better on a particular object. But in the majority of cases, the excitability is not uniform. Depression soon follows excitement with lessened sensitiveness to pain and other disturbing factors thus promoting a dreamy, abstracted state of mind conducive to sleep. After waking, there is a feeling of headache and nausea. In this stage, the higher psychical centres are first depressed and then the lower ones. In fact

opium acts on the cerebral centres in the reverse order of their development and forms an illustration of the "law of dissolution." Hearing, sight and cutaneous sensibility become blunted, and the sleeper feels no pain. Opium therefore resembles alcohol or chloroform in its effects on the central nervous system, but its action is directed more to the respiration and pain sensation, both of which are depressed in doses which have little effect on general consciousness. In fact morphine has a specific action in relieving pain in non-narcotic doses which it does by depressing the tracts by which the pain sensations reach the consciousness. If the dose is large, the excitement is only momentary or absent. Coma soon supervenes with a profound depression of the cerebrum and reflex excitability.

The medullary centres are affected by morphine; the vagal and the vomiting centres are stimulated, while the respiratory and the cough centres are depressed. The vaso-constrictor centre is slightly stimulated but the vessels of the skin and head and neck region dilate. In large doses however there is depression of the vomiting centre so that no emesis occurs even after large doses of emetics. The oculomotor centre is stimulated causing contraction of the pupil.

Because of the depressant effects on the brain morphine is valuable as a pre-anæsthetic hypnotic and is given prior to an operation to relieve the patient's anxiety and to render him indifferent to subsequent happenings. It also potentiates the action of volatile anæsthetics when it is often given with atropine to reduce salivary secretion.

While depression of the central nervous system is marked in morphine poisoning in man, its effects on lower animals are peculiar. Thus in cat it causes wild delirium, restlessness and excitement for a considerable time before any signs of narcosis appear. In dogs the cardio-inhibitory centre is stimulated, and convulsion, vomiting and purging follow. As a rule relatively larger doses are required to elicit any effect in lower animals than in man.

Spinal cord.—Both morphine and opium, more particularly the latter, increase the reflex excitability of the cord. In lower animals, e.g. frogs and cats, this is more marked and may be followed by convulsion of the strychnine type. In man the reflexes are depressed, but no muscular relaxation is noticed as happens after chloral or bromides. Sometimes however it produces convulsion in man, but how far this is due to asphyxia or to morphine is difficult to say.

Nerves and muscles.—The motor and sensory nerves are not affected except in very large doses. There is no complete loss of muscular power or irritability, for even in severe opium poisoning, the patient can be made to walk if supported. Because of sluggish cerebral activity and diminished perception voluntary movements are diminished.

Uterus.—Barbour has shown that in therapeutic doses opium has no effect on normal uterine contraction of the animal. During labour it delays its progress because of the sedative action and by preventing reinforcement of labour pain by the contraction of the abdominal muscles. Its use may be of value in checking threatening abortion from its sedative effect on the uterine muscle.

Temperature.—It reduces temperature by loss of heat from dilated peripheral vessels, diaphoresis, and partly from diminished movements by which less heat is formed.

Eye.—In morphine poisoning the pupils are contracted to a pin point, and they are contracted even in small doses. The effect lasts till asphyxia sets in when they are widely dilated. This effect disappears when the oculo-motor endings are paralysed by atropine, but it is not affected by cocaine which stimulates the sympathetic endings. The action is central, since when dropped into the eye or injected into the excised eye it has no effect. It has been suggested (Mayer and Gottlieb) that it depresses the inhibitory impulses which normally keep the oculo-motor tone in abeyance. The intra-ocular tension is increased.

Kidneys.—The secretion of urine is not affected by opium, although there is some retention of urine from spasm of the sphincter of the bladder in toxic doses, though it may also occur even in therapeutic doses. Morphine is found unchanged in the urine. There is a chance of morphine being reabsorbed from the bladder. The amount of sugar in diabetic urine, and that of urea according to some authorities, are diminished.

Skin.—Opium is a diaphoretic, acting by directly stimulating the sweat glands, and by dilating cutaneous vessels even in small doses. Before death there is copious perspiration due to asphyxia. It may cause itching and a rash.

Secretion.—It diminishes every secretion of the body except that of the skin and the mammary glands.

It may cause poisoning through milk to suckling babies, and since it passes through the placental circulation to the fetus, the latter may be killed in utero.

Absorption and elimination.—Morphine is rapidly absorbed from all mucous surfaces and abraded skin. Its absorption from the intact skin is doubtful. From the blood the drug absorbed passes into the tissues where it is temporarily stored. Part of it is destroyed, rest is excreted through the faeces and urine. It is excreted by the gastro-intestinal tract even when used hypodermically and continues to be found in the stomach all through the period of morphine action. Traces have also been found in the milk and sweat. The amount excreted with the urine is less at the beginning when most of the alkaloid is found in the stomach. Later it is increased.

Toleration—It is well-known that continued use of opium or morphine induces tolerance of the drug so that larger doses are necessary to elicit the desired effect. Moreover the patient can take quite a large dose without showing any untoward symptom. The same tolerance of the drug can be developed in animals (except rabbits), notably in monkeys, cats and dogs. The mechanism which enables the addict to tolerate large doses has not been clearly explained. It is possible that more than one factor is responsible for this phenomenon. It may be either storage of the alkaloid in the muscles, or increased power of the tissues to destroy the alkaloid. The view that it is stored as oxydimorphine is not accepted as it has been shown that this compound is not formed. Similarly the idea that it helped the formation of antitoxin may also be dismissed as it has been found that the blood of habituated animals contained neither protective nor toxic substances. Several workers have reported increased destruction of the alkaloid but it is doubtful whether this plays any important part in the production of tolerance.

Acute toxic action.—Poisoning by opium is very common in India especially in Bengal. It is chiefly suicidal, and is more frequent amongst the Indians. In most cases it is mixed with oil before swallowing. Excitement in such a case is very brief or none at all. Drowsiness and stupor soon follow. The patient may be roused at first, but soon passes into profound coma, and no external stimulus can rouse him then. The pupils contract to a pin's point, surface becomes cold and clammy; face and lips livid; pulse very weak and slow; respiration slow, irregular and at the end stertorous; finally the patient dies from asphyxia. A few minutes before death, pupils dilate. P.M. appearances are like those of suffocation.

Treatment.—If opium or morphine is swallowed, wash out the stomach with stomach-pump, emetics generally fail after absorption owing to depression of the centre. Potassium permanganate is a chemical antidote and its solution (4 to 8 grs. in 4 to 8 ozs. of water) should be given at once if the quantity of poison is unknown or large, before washing. A weak solution should be employed as a wash for the stomach. The special danger is the failure of respiration, therefore respiratory stimulants in the form of hot black coffee (caffeine) should be used. Atropine $\frac{1}{2}$ gr. should be given to excite the centre but in larger doses it tends to weaken the respiration. Carbon dioxide and oxygen inhalation. Strychnine $\frac{1}{8}$ gr. hypodermically, repeated every 2 or 3 hours for heart and lungs. Similarly, artificial respiration. Alternate cold and hot affusions, flagellations, or taps upon the forehead with finger-nails, sinapism, electricity, smelling salts to the nose, and making the patient walk to and fro, should be adopted to keep the patient awake. The treatment is to be kept up for several hours until the danger is over. Some recommend washing the stomach now and then as opium is excreted in it, but that is unnecessary, as the quantity is infinitesimal and the exhaustion is rather overmuch.

Chronic toxic action or Morphinomania—Persons soon get habituated to the use, and can consume large quantities. It is therefore necessary that the patient should remain ignorant of the drug. India, Turkey, Persia, and China, are the principal countries where the drug is habitually indulged in. Morphinomania exists also in England. In India opium is either eaten or smoked. Moderate doses (5 to 20 grs.) daily do no harm, but *madak* and *chandu* smokers are a dis-

reputable set. Moral depravity, emaciation, anæmia, muscular weakness, physical depression, feeble and small pulse, tremor, slight ataxy, loss of appetite, indigestion, sluggish bowels, insomnia, drowsy feeling, sexual impotence, amenorrhœa, small pupils, are the principal symptoms of morphinomania.

Treatment.—*Gradual* reduction is the best plan. Tea, cocoa, ammonia may be given to ward off depression and collapse. Sometimes small doses of alcohol may be necessary. If an opium-eater be suddenly deprived of his accustomed dose of the drug, cerebral excitement, restlessness, pain in the stomach and a burning sensation in the back give great trouble. There may be vomiting, diarrhœa, perspiration, seminal emission in male, and orgasm in female.

Diagnosis of opium poisoning—This falls under the province of medicine. However, a few hints will enable the reader to form a correct diagnosis (1) **Alcoholic coma**—Take a careful *history*. *Smell of breath* may not help always, as the opium and alcohol may be taken together or one after the other, or some one may have given it later. *Pupils* are contracted in opium poisoning, and normal or dilated in alcoholic poisoning. *External stimulus* rouses the patient more readily in alcoholic coma than in opium poisoning. *Stomach-pump* will guide in some cases. (2) **Cerebral hæmorrhage**.—*History*. *Pupils* are unequally contracted but if the hæmorrhage is in the pons, they may be contracted and render the diagnosis more difficult. *Paralysis* of limbs occurs on one side. *Temperature* generally falls in the beginning and then rises. (3) **Uræmia**.—*Coma* less profound. *Albumin* in the urine. Sometimes convulsions alternating with coma. Examine for *hypertrophy of the left ventricle*, *arterio-sclerosis*, and *retinal changes*. (4) **Diabetic coma**, by the breath and the presence of *sugar* and *diacetic acid* in the urine. (5) **Epileptic coma** after a fit, *coma* less profound, dilatation of pupils. Examine for *Babinski's sign*. (6) **Hysterical stupor** by its characteristic symptoms and history. (7) **Chloroform, ether, and carbolic acid poisoning**, by smell and other special symptoms.

Modifying influences.—Many circumstances modify the action of opium. (1) **Age**.—Children are more susceptible to poisoning. An infant under one year should not have more than $\frac{1}{4}$ to 1 m. of the tincture. (2) **Sex**.—Women suffer more from after-effects than men. To a nursing mother it must be given with caution. (3) **Idiosyncrasy**.—Some cannot take opium without brain symptoms, such as insomnia or delirium, while others suffer from gastric irritation. The writer had to treat a woman in whom morphine $\frac{1}{4}$ gr. given hypodermically produced fainting, vomiting, and collapse. (4) **Habit**.—Toleration is readily induced, when large doses become necessary to produce the desired effect and gradually lead to *opium habit*. The writer knew a person who used to take 40 grs. of morphine daily. (5) **Diseases**.—Acute painful diseases require larger doses. Subjects of Bright's disease cannot bear much opium, and it should be given to them with great caution, also to persons suffering from cardiac, pulmonary, and other renal diseases, cerebral congestion, and alcoholism. (6) **Drugs**.—Chloral hydrate, potassium bromide, chloroform, etc., increase its soporific virtue, while belladonna removes constipation when given in combination.

Difference of action between opium and morphine.—Though the description of the pharmacology of opium given in these pages applies also to that of morphine, yet there are certain differences, which are detailed below:—

Opium	Morphine
1. Preparations less soluble, slowly absorbed. Action slow, but more lasting	Preparations more soluble, readily absorbed, action quicker, but not so lasting.

Opium	Morphine
2. Its several constituents, such as thebaine, codeine, narcotine are convulsants.	Morphine not so in man.
3. Action variable on account of varying composition.	Action definite on account of definite composition.
4. Constipation, nausea, and indigestion more frequent.	Constipation, nausea, and indigestion less frequent.
5. Better diaphoretic	Feeble or no diaphoretic.
6. Less sedative and less soporific.	More sedative and more soporific.
7. Greatly reduces the sugar of diabetic urine.	No appreciable effect.
8. Local action more marked on the intestines.	Less marked on the intestines.
9. Cannot be administered hypodermically.	Can be administered hypodermically.

Antagonists.—Atropine, caffeine, cocaine, physostigmine, and strychnine are antagonistic to some action or other of morphine. The antagonism between morphine and atropine is given below in detail:—

	Morphine	Atropine
Real	1. Cerebral convolutions depressed.	Cerebral convolutions stimulated.
	2. Respiratory centre depressed.	Respiratory centre stimulated.
	3. Intestinal peristalsis depressed causing constipation.	Intestinal peristalsis regulated. No constipation.
Apparent	4. Stimulates the vagus centre and <i>slows</i> the pulse.	Depresses the vagus nerve endings and <i>quickens</i> the pulse.
	5. <i>Pupils contracted</i> through the effect on the pupillary centre.	<i>Pupils dilated</i> through the paralysis of the third nerve endings.
	6. <i>Diaphoretic</i> by specifically dilating the cutaneous vessels.	<i>Anhydrotic</i> through the terminal nerves in the glands.

Though morphine and atropine are not true antagonists, yet they are useful antidotes to each other in poisoning. They are therefore partial antagonists and are used in combination to avoid certain untoward results of morphine without losing the useful effects. They are useful in combination in renal and hepatic colic, both of which relieve spasm, and atropine obviates the nausea which follows the use of morphine alone.

Action of other opium alkaloids.—The important alkaloids are, morphine, narcotine, papaverine, codeine and thebaine. Of these morphine, codeine and thebaine are *phenanthrene derivatives*, while papaverine and narcotine are *isoquinoline derivatives*. The latter group are depressants to the smooth muscles.

Papaverine is a powerful antispasmodic and relaxes all involuntary muscles specially when spasmodically contracted. Lowers blood-pressure from vaso-dilatation of the splanchnic area. The action on the central nervous system is between codeine and morphine. It stimulates the respiratory centre. Small doses induce sleep, but large doses do not make it deeper. Not an analgesic. *Narcotine* resembles more papaverine in relaxing the plain muscles. *Thebaine* is not a depressant but is a convulsant like strychnine through its effect on the cord; it is however less active than strychnine.

THERAPEUTICS

Externally.—Opium is chiefly used as a local sedative and anodyne. Hot poultices or fomentations containing opium or with laudanum sprinkled, are often employed to allay the pain of pleurisy, rheumatism, peritonitis, lumbago, inflamed joint, etc. *Earache* is relieved by laudanum mixed with equal amount of glycerin. Opium or morphine suppository, and the gall and opium ointment often allay the pain of anal fissures and piles. Opium injection *per rectum* relieves rectal tenesmus, urethral spasms, or pelvic pains. Neuralgic pains are better relieved when morphine is used hypodermically.

Internally.—Opium is a remedy *par excellence* for removing pain, subduing excitement and irritation, and inducing sleep.

Mouth and stomach.—Opium or morphine allays gastric pain. Thus it is very useful in ulcer, cancer, and gastritis produced by alcoholism. Morphine with bismuth markedly relieves gastrodynia with or without heartburn.

Intestines.—Of all the drugs we have for diarrhœa opium is the most valuable both in the acute, chronic and tubercular varieties. In lenteric diarrhœa where the half-digested food is simply swept down the canal by the excessive peristalsis, opium acts remarkably well. It is desirable to administer one or two doses of opium in diarrhœa or dysentery after the expulsion of the offending matters. It is usually combined with bismuth in diarrhœa* and castor oil in dysentery. In the early stage of cholera, especially when preliminary diarrhœa is the prominent symptom, opium may be usefully employed,† but not in the cold stage. In typhoid fever it serves a double purpose by controlling wakefulness and delirium and subduing diarrhœa. A rectal injection of starch and opium may sometimes relieve where the ordinary method of administration by the mouth has failed, especially in dysentery. It relieves intestinal colic caused by sharp aggravated contractions of the bowels.

Enema Opii (0.5 to 6 p.c. in mucilage of starch) 2 to 4 oz. is serviceable in various ways, by checking flux, subduing local irritation, pain and spasm of the rectum and neighbouring structures, and giving rest to the pelvic organs. A morphine suppository generally averts a rigor likely to follow catheterisation or abdominal operations. To soothe local pain, an ordinary dose is enough for rectal injection, but a large dose is required to induce sleep.

Heart and blood-vessels —Opium, preferably morphine,

*R

Bism. carb.	grs. 10
Pulv ipecac et opii	grs 5
Pulv cret. aromat.	grs 10
In diarrhœa	

†R

Acid sulph. aromat	ms 10
Tinct. chlorof et morph. co	ms 5-10
Syr zingib	ms 30
Aqua menth pip dest	ad oz. 1
In early stage of cholera	

is sometimes used in diseases of the heart. There can be no question that unmistakable relief is afforded by morphine injection in the dyspnoea of heart disease and of blood-vessels, and in angina pectoris. A single injection of $\frac{1}{2}$ gr. brings on refreshing sleep from which the patient wakes wonderfully revived; but it should not be used in cardiac dyspnoea caused by the pressure of serous and dropsical fluid. If the kidneys are diseased opium is said to be contra-indicated though many recommend the administration of morphine $\frac{1}{2}$ gr. subcutaneously in renal dyspnoea and uræmic convulsions. Atropine may be usefully combined to counteract the depressing influence.

Morphine is an excellent hæmostatic in internal hæmorrhage specially in intestinal and pulmonary bleeding. In the former, it is of special value because of its special action on the movements of the intestine; and in the latter, it not only slows the heart and reduces blood-pressure, but lessens cough, produces sleep, and removes mental anxiety.

Respiratory tract—Opium relieves *cough* but should be used with caution. When the cough is harassing and frequent, without much expectoration and without any tendency to asphyxia or lividity, due to reflex irritation or from excessive irritability of the nerves as in pleuritis, opium is justly and admirably indicated. But, when the act of coughing is only to empty the bronchial tubes of the abundant secretion, as in the bronchitis of the aged and infirm, or of the weak and young, opium is positively injurious; for it leads to inspissation and retention of the mucus. In phthisis where the tubercles press upon the nerves, and give rise to reflex cough, opium may be given with benefit. In the same way, by the local application of morphine to the throat, in the form of linctus (*see* p. 174) and lozenges, many reflex coughs can be relieved. Sometimes it gives marked relief to the spasm in **whooping cough**; $\frac{1}{4}$ to 2 ms. of the linctus every hour, or $\frac{1}{50}$ gr. of morphine every 3 or 4 hours, according to the age of the child, should be continued until the whoop disappears. It should be given with great caution in **asthma**, lest it should create an opium habit, but instances are common where the habitual use of opium cured asthma. The sharp stitch of **acute pleurisy** or **pleuro-pneumonia** is relieved, as if by a charm, with a hypodermic injection of morphine. It may be used in the early stage of pneumonia to relieve pain and distress, but should be avoided in the later stage specially when there are signs of respiratory failure. A dose of Dover's powder often cuts short an attack of acute coryza and gives relief in influenza when taken with acetylsalicylic acid.

Nervous system.—As a hypnotic, pure and simple, morphine is inferior to chloral hydrate, but for sleeplessness due to pain or irritation, it is a sovereign remedy. It is

often used in the insomnia of acute diseases, in mania and alcoholism, and in the restlessness of visceral diseases. But the gradual tendency nowadays is in many of these diseases to combine it with chloral hydrate, either alone or with the addition of bromides, especially so in mania and delirium tremens. Its superior value as an **anodyne** has been long recognised. A hypodermic injection of morphine ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) relieves biliary, lead and intestinal colics; sciatica; facial, and other kinds of neuralgias; and severe pleurodynia. The pain of fractures, dislocations or other injuries, of acute rheumatism, dysmenorrhœa and malignant diseases are only a few instances where opium or morphine can be most usefully employed. In short any pain, inflammatory or otherwise, is relieved by opiates. It is to be noted that sufferers from pain can consume large quantities without poisoning.

As an antispasmodic in convulsive diseases it has been used in tetanus and other forms of convulsions, such as chorea and epilepsy, but it is doubtful if it is of any use in these diseases since morphine itself increases reflex excitability. Moreover its depressant effect on the respiration should be kept in mind. In these diseases drugs of the chloral group or any of the barbiturates are preferable. The pains and spasms of certain diseases of the cord, such as locomotor ataxy, are subdued by the subcutaneous injection of morphine.

It is valuable as a **pre-anæsthetic hypnotic** (see page 166) and is sometimes used to **prolong chloroform anæsthesia**, and when combined with scopolamine produces sufficient anæsthesia, to perform operations. For this purpose morphine $\frac{1}{2}$ gr. and scopolamine $\frac{1}{200}$ gr. is given in two injections. This combination has also been used during labour, the so-called "twilight sleep."

Kidneys.—As morphine is not rapidly eliminated by the diseased kidneys, it should be given with caution in Bright's disease, for instances have occurred where small doses have produced fatal results. But a hypodermic injection of $\frac{1}{4}$ gr. of morphine has occasionally been found to remove uræmic insomnia, uræmic convulsions and uræmic or cardiac dyspnoea, and one is justified in taking this risk under these conditions. As they reduce the sugar in diabetic urine, opium and codeine are used in **diabetes mellitus**.

Skin.—As a diaphoretic, Dover's powder is used in a

R̄

Pot bicarb	grs 10
Tinct opii camph	ms 20
Sp ammon aromat.	ms 20
Syr. prun serotina	ms 30
Aqua chlorof	ad oz. 1
In chronic bronchitis and cough.	

R̄

Ammon. chlor.	gr 5
Tinct ipecac	ms. $7\frac{1}{2}$
Tinct opii camph	ms 20
Syr scull.	ms. 30
Aqua chlorof.	ad oz. 1
In bronchitis.	

variety of diseases, such as cold, influenza and slight inflammatory conditions.

Uterus.—Opium is invaluable in arresting a threatening abortion. It must be given in large doses, laudanum in 20 or 30 ms., or the extract in 1 gr. doses every 3, 4 or 6 hours, as indicated. In normal labour its use should be confined to the first stage. In later stage it is better avoided as there is risk of depressing the respiratory centre of the child. It is also used to relieve after-pains.

Malaria.—It is a fact that opium-eaters are less liable to malarial poisoning, and they enjoy better health in malarial districts. Opium occasionally cures malarial fever where quinine fails, or the two drugs combined are more successful than either given alone. This effect is possibly due to *narcotine* which is used in chronic cases either alone or with quinine. The writer has seen a few cases of filarial fever checked by the habitual use of opium.

Mode of administration.—Opium or morphine can be administered by (1) the *mouth* as pill, powder and mixture; (2) *per rectum*, as suppository or enema; (3) *enepidermically*, as plaster; (4) *epidermically*, as liniment; (5) *hypodermically*, when the pain is very severe, such as colic or neuralgia.

Contra-indications.—It should not be used in

- (a) cedema of the lungs, and Cheyne-Stokes breathing;
- (b) inflammatory and congestive state of the central nervous system, *e.g.* meningitis, fever, in overwork and in cerebral congestion with a tendency to apoplexy;
- (c) acute dilatation (paralysis) of the stomach or bowels; and *used with caution* in
- (d) nephritis, especially when there is a tendency to uræmia;
- (e) infancy and old age; and
- (f) in all chronic painful diseases on account of the risk of formation of habit.

C EINA

(Codein)

Codeine. $C_{18}H_{21}NO_3, H_2O$

Syn.—Methylmorphine, U.S.P.

Source.—It is morphine methyl ether, an alkaloid obtained from opium, or prepared by the methylation of morphine.

Characters.—Colourless, translucent crystals, or a crystalline powder; odourless; taste, bitter. *Soluble* in 120 parts of water, readily in alcohol (90 p.c.), in 20 parts of ether, freely in chloroform.

B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.016 to 0.06 grm.

C EINAE P OSP AS

(Codein Phosph)

Codeine Phosphate. $C_{18}H_{21}NO_3, H_3PO_4, H_2O$

Source.—The phosphate of the alkaloid codeine.

Characters.—Colourless, acicular crystals, or a crystalline powder; odourless; taste, bitter. *Soluble* in 3.5 parts of water, in 350 parts alcohol (90 p.c.), sparingly in ether and chloroform.

B.P. Dose.— $\frac{1}{4}$ to 1 gr or 0.016 to 0.06 grm.

NON-OFFICIAL PREPARATIONS

1 *Linctus Codeinæ*, B P C.—Codeine Phosphate $\frac{1}{8}$ gr. in 1 dr. Syrup of codeine phosphate 50, citric acid 175, emulsion of chloroform 5, glycerin 1650, mucilage of tiagacanth q s to 100. *Dose*.— $\frac{1}{2}$ to 1 dr or 2 to 4 mls

2 *Codeinæ Sulphas*, U S P.—Colourless crystal, usually, needle-shaped, or a white crystalline powder Efflorescent *Dose* U S P.— $\frac{1}{2}$ gr or 0.03 grm

3 *Apocodeinæ Hydrochloride*—A greyish powder soluble in water Sedative and *increases intestinal peristalsis* by depressing sympathetic endings, therefore antagonises the action of atropine. *Dose* — $\frac{1}{10}$ to 1 gr. or 0.006 to 0.06 grm

4 *Dicodid*—Dihydrocodemone acid tartrate. Similar to dilaudid. Also makes the respiratory centre less sensitive to CO₂ *Dose* — $\frac{1}{16}$ to $\frac{1}{12}$ gr or 0.004 to 0.005 grm.

5 *Syrupus Codeinæ Phosphatis*, B P 1914—Codeine phosphate, 5 grm., distilled water, 20 ml., syrup, q s 1000 ml. Strength $\frac{1}{4}$ gr. in 1 dr. *Dose* — $\frac{1}{2}$ to 2 dr. or 2 to 8 mls.

PHARMACOLOGY

Internally.—Codeine is a feeble narcotic, because it does not depress the cerebral convolutions so actively as morphine, but it excites the cord more. It is therefore inferior to morphine in relieving pain and producing sleep. It does not produce nausea or vomiting, but causes constipation. It does not cause a habit, and is less depressing to the respiration than morphine, but it will relieve cough in doses insufficient to relieve pain. It is a great paralyser of the visceral nerves, for it has been found that after its administration, irritant poisons, such as arsenic, produce neither vomiting nor purging. Codeine decidedly excites the spinal cord producing muscular tremor and increased reflex excitability when used in slightly beyond the hypnotic doses. It lessens the amount of sugar in diabetes.

THERAPEUTICS

Internally—On account of its sedative influence on the visceral nerves, it soothes the hacking cough of phthisis and visceral neuralgia. Syrupus codein. phosph. in 1 to 2 dr. doses, alone or with syrup of wild cherry, is a good preparation for allaying cough. Sometimes it is used with advantage in insomnia due to pain in some peripheral regions, when it should be given in 1 or 2 gr. doses, every 4 or 6 hours, till sleep comes on. But its chief use is in the treatment of diabetes mellitus* in which case it can be given in the form of a pill. The phosphate being more soluble than the alkaloid can be used in a mixture. It is highly efficient in abdominal and pelvic pain, specially when ovarian in origin.

Apocodeine resembles apomorphine in its action, but is

*R

Codein phosh gr. $\frac{1}{2}$

Ext. nuc vom. gr. $\frac{1}{4}$

Ext bellad sic gr. $\frac{1}{4}$

Pil thei co. grs 4

a better expectorant and less efficient emetic than the latter. 30 ms. of a 1 p.c. solution is used in bronchitis, and the same amount when used hypodermically acts as a purgative.

DIAMORPHINE HYDROCHLORIDE

(Diamorph. Hydrochlor)

Diamorphine Hydrochloride. $C_{21}H_{23}O_5N, HCl, H_2O$

Syn.—Heroin Hydrochloride : Diacetyl-morphine Hydrochloride.

Source.—The hydrochloride of an alkaloid obtained by acetylation of morphine.

Characters.—A colourless, crystalline powder; taste, bitter. *Solubility*.—1 in 2 parts of water, 1 in 11 parts of alcohol (90 p.c.).

Incompatibles.—Acids and alkalis which decompose it.

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{4}$ gr. or 0.0025 to 0.008 grm.

NON-OFFICIAL PREPARATIONS

1 Elixir Diamorphinæ et Pini Co., B.P.C.—Each dr contains $\frac{1}{32}$ gr diamorphine hydrochloride, and $\frac{5}{16}$ gr. terpin hydrate with oil of pine, glycerin, etc. Dose.— $\frac{1}{2}$ to 1 dr. or 2 to 4 mls

2 Elixir Diamorphinæ et Terpini cum Apomorphina, B.P.C.—Contains $\frac{1}{16}$ gr heroin hydrochlor, $\frac{5}{16}$ gr terpin hydrate and $\frac{1}{32}$ gr. apomorphine hydrochloride in 1 dr Dose.— $\frac{1}{2}$ to 1 dr or 2 to 4 mls.

3 Linctus Diamorphinæ cum Ipecacuanha, B.P.C.—Contains $\frac{1}{16}$ gr heroin hydrochlor, $\frac{3}{4}$ m liquid extract of ipecac, in 1 dr, with hyoscyamus. and syrup of tolu. Dose.— $\frac{1}{2}$ to 1 dr or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Heroin resembles morphine in its general action, which it has replaced in the treatment of cough, especially the dry hacking cough of phthisis. It is a depressant to the respiration, which is rendered slower but deeper, but it does not interfere with gas exchange, and is used to stop irritable cough. It is about five times more depressant than morphine, but less so to sensory nerves and not so constipating. A hypodermic injection often relieves a fit of asthma. For the relief of cough it is generally used in the form of linctus. It is liable to produce a 'habit' and causes suppression of urine, and has no advantage over morphine or codeine.

CANNABIS INDICA

Indian Hemp. (Cannab. Ind.). (Not official)

Syn. I.V.—*Ganja*. Beng, Hind

Source.—The dried flowering or fruiting tops of the pistillate plants of *Cannabis sativa*, grown in India, from which no resin has been removed

Composition—(1) An active Resin (*cannabinone*), the chief constituent of which is *Cannabinol*, $C_{21}H_{35}O_2$ (2) A Volatile Oil Fat, wax, etc

Incompatibles—Water and watery infusions precipitate the resin.

NON-OFFICIAL PREPARATIONS

1 Extractum Cannabis—A rich green, soft resinous extract Dose.— $\frac{1}{4}$ to 1 gr or 0.016 to 0.06 grm.

- 2 Tinctura Cannabis —1 in 20 of extract Dose —5 to 15 ms or 0.3 to 1 mil.
 3. Cannabinæ Tannas —A brownish powder In *dysmenorrhœa*, *menorrhagia*,
 and as a *hypnotic* in nervous insomnia Dose.—4 to 8 grs or 0.25 to 0.5 grm.

PHARMACOLOGY OF CANNABIS INDICA

Internally.—In small doses it sharpens the appetite, which becomes sometimes so ravenous that it cannot be appeased by food. It also promotes digestion and causes constipation. If indulged in for long it may cause loss of appetite and gastric derangement. It is slowly absorbed by the small intestine and produces its effects within half an hour. It relieves spasm of the intestine.

Nervous system.—Its chief action is on the cerebrum and resembles in many respects that of alcohol or opium, but is uncertain owing to variation in strength and to individual peculiarities. When smoked the effects are almost instantaneous. In small doses, either smoked or taken by the mouth, it causes pleasurable sensations with gay, joyful and exalted ideas and a refreshed feeling, specially after bodily fatigue. In fact it is often smoked by some people to enable them to undergo physical exertion without appreciation of fatigue or exhaustion. Ganja smoking is almost universal with certain classes of *sadhus* and *mendicants* and it is said it helps them to forget all about their worries and privations of the outside world, and concentrate their mind in an agreeable manner to their devotion. Under its influence the knowledge of time and personality is lost and the drugged man feels that he is enjoying the pleasures of life for hours together, although in reality it is only for a few minutes. If continued, it causes intoxication and loss of self control. The drugged man becomes very talkative and jovial, and laughs at every thing, whereas a sedate person becomes more sociable, has less control over himself, and eventually passes into a sort of waking delirium. The delirium, generally noisy and restless, is accompanied by muscular excitement, and is followed by sleep which is attended with delightful and erotic dreams. It is therefore an *exhilarant*, *deliriant* and *hypnotic*. Sometimes there is considerable amount of heaviness in the head and the patient feels "a sensation as of the brain boiling over and lifting the cranial arch." In large doses it induces a sort of catalepsy, followed by coma and death from cardiac failure. Excessive smoking of ganja, specially by beginners may cause mental derangement and even insanity.

The sensory nerves are paralysed and there is tingling and anæsthesia of the skin. The muscular sense is also lost, and if pain is present is abolished or at least reduced. It is an *anodyne* but less so than opium or belladonna.

Heart and circulation.—Its action here is very uncertain. The pulse may be quickened or slowed depending upon excitation or narcosis.

Respiration is not affected. The breathing becomes hurried during the stage of excitement. The pulse is not altered when taken as a drink, but becomes slow during narcosis.

The secretion of urine is slightly increased, but prepared *bhāng*, which is used as a drink, causes copious diuresis.

In the form of *ganja*, hemp is largely smoked, and the leaves are used by powdering it and mixing with aromatics, sugar, cardamom and milk, and the preparation is then known as *bhāng*, *sidhi*, or *sabji*. *Charas* is of a dark green or brown colour and contains resins which exude from the leaves, is as a rule smoked with tobacco, and is a powerful narcotic. The leaves are also used in the preparations of different kinds of sweets and pastries, and the prepared *bhāng* is also taken as ice-creams. They all produce the same effects on the central nervous system. *Hashis* is a confection and contains in addition to the leaves and resins, opium, poppy seeds, datura seeds, cloves, anise, sugar, butter, milk, etc.

THERAPEUTICS OF CANNABIS INDICA

Externally.—Mixed with linseed meal (1 in 4), hemp in the form of poultice allays the irritation and pain of inflamed piles and fissures. The dry leaves warmed may be used as fomentation for the same purpose.

Internally Gastro-intestinal tract.—As an appetiser and stomachic tonic it is valuable in dyspepsia and dyspeptic diarrhoea, and relieves pain and spasm in some forms of dysentery specially when combined with small doses of castor oil. It soothes the pain of gastralgia and corrects the griping of purgatives.

Nervous system.—As an *analgesic* it was largely used in migraine but is not much used now being replaced by the drugs of the phenacetin group. It is occasionally used with benefit in continuous headaches, specially those occurring at the menopause, or due to worry and fatigue. As a hypnotic it is rarely used now although Sir Russell Reynolds strongly recommends the extract ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) in senile insomnia. As an anodyne antispasmodic, the tincture or the extract may be used in intestinal, biliary and renal colics, spasm of the bladder and chordee. Its beneficial effects in tetanus has long been recognised.

Genital organs.—In menorrhagia, spasmodic and nervous dysmenorrhoea and ovarian irritation, it not only relieves the pain, but seems to act favourably on the uterine muscular fibres.

2. ALIPHATIC HYPNOTICS

(a) Chloral Group

CHLO ALIS Y AS

Chloral Hydrate. (Chloral Hydr.). $\text{CCl}_3\text{CH}(\text{OH})_2$

Source.—Obtained by the addition of water to chloral, produced by the action of dry chlorine on ethyl alcohol.

Characters.—In colourless, non-deliquescent crystals. Odour, pungent but not acrid. Taste, pungent, bitter. Volatilises slowly on exposure to air. *Solubility.*—Less than in 1 part of water, alcohol (90 p.c.), ether, and in 3 parts of chloroform.

Incompatibles.—Alkaline substances which liberate chloroform.

B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 gm.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

- 1 Chloral Camphoraturn, B.P.C.—Each equal amount
- 2 Syrupus Chloralis, B.P. 1914.—Each fluid dr. contains about 11 grs. of chloral hydrate *Dose*—30 to 120 ms or 2 to 8 mls.
- 3 Dormiol *Syn*—*Amylene Chloral*—A colourless liquid with camphoraceous odour *Dose*—5 to 50 ms or 0.3 to 3.5 mls.
- 4 Butyl-chloral Hydras—In pearly white trimetric laminae, with a pungent, acid odour and an acid taste. Action similar to chloral hydrate, supposed to be specially valuable in neuralgia of the 5th nerve *Dose*—5 to 20 grs. or 0.3 to 1.2 gm.
- 5 Glucochloral, B.P.C. *Syn*—*Chloralose*—A hypnotic, resembles more morphine than chloral. Produces, increased reflexes and sometimes convulsion, specially when large doses are given. Heart is not affected nor the respiration unless given in large doses. *Dose*—3 to 10 grs. or 0.2 to 0.6 gm.

PHARMACOLOGY

Locally chloral is an irritant to the skin and when used in a concentrated solution may even cause vesication. It is an antiseptic.

Internally.—Chloral is an irritant to the stomach and in

concentrated solution causes nausea and vomiting. Given freely diluted no such effect is observed. It is readily absorbed and carried to the central nervous system where it is taken up by the cells. It is reduced in the body into trichlorethyl alcohol, which also acts as a hypnotic.

Heart and circulation.—A moderate dose of chloral (10 to 20 grs.) in a healthy adult rarely causes any circulatory changes except that the heart is rendered slow, but this is not more than is found in natural sleep. In common with all narcotics containing a halogen derivative, it depresses the heart and finally arrests it in diastole, but this effect is only observed when the dose is above the therapeutic limit. This is due to its direct action on the cardiac muscle. The blood pressure is not affected in ordinary therapeutic doses, but there is some flushing of the skin from dilatation of the cutaneous vessels, and for this reason there may be skin eruption forming erythematous rash, although may be urticarial or purpuric. In large doses, or in poisoning, the pressure falls from diminished cardiac output and depression of the vaso-motor centre causing dilatation of the vessels, when the pulse becomes slow, feeble and intermittent.

Respiration —In moderate doses no effect on respiration is observed, but in toxic doses the breathing becomes slower, shallower and irregular, and finally stops from paralysis with the simultaneous arrest of the heart.

Temperature.—Chloral hydrate tends to lower the body-heat, and in toxic doses there is a marked diminution of the temperature, due to dilatation of the cutaneous vessels and diminished production of heat from muscular relaxation, and possibly to diminished activity of the heat regulating centre.

Cerebrum.—In moderate doses (15 to 30 grs.) it induces within ten to fifteen minutes a sort of soothing drowsiness followed by refreshing sleep indistinguishable from natural slumber. The sleep generally lasts from 5 to 8 hours without producing any unpleasant after-effects, such as, headache, drowsiness, confusion or sickness. It induces sleep by depressing the sensory or receptive functions of the brain. And since the sleep is induced by dulling of the perceptions, acute pain may prevent sleep after chloral. In fact chloral has no effect in relieving pain like opium. Large doses (50 to 80 grs.) cause prolonged sleep which is deeper, and although no complete anæsthesia is produced, pain is less felt and the reflexes are lessened. Still larger doses produce stupor and coma with complete muscular relaxation leading to asphyxia from paralysis of respiration. Before death the pupils are powerfully contracted to pin point. The motor areas of the brain cortex are rendered less irritable which eventually fail to react to electrical stimulation.

Spinal cord.—In ordinary hypnotic doses the spinal reflexes are not affected. In large doses they are first

depressed and then paralysed before the failure of respiration. This effect on the spinal reflexes is more marked than morphine.

Kidneys.—It is excreted by the urine in combination with glycuronic acid which reduces Fehling's solution and therefore it was thought that chloral caused glycosuria. Large doses cause nephritis and hæmaturia.

Absorption and elimination—It is absorbed from all mucous surfaces and excreted with the urine as non-toxic trichlor-ethylglycuronic acid (urochloralic acid). It has less tendency to cumulative effect. A portion is eliminated unchanged. It escapes chiefly by the kidneys and partly by the lungs and skin.

Acute toxic action.—Acute poisoning is rare. The symptoms are profound sleep merging into deep coma; lividity of the face; pallor; cold sweat over the forehead and head; slow, laboured, and afterwards shallow and feeble breathing; frequent, feeble, and irregular pulse; *marked fall of temperature*, which may be so great as alone to cause death (Brunton); pupils contracted and absolute muscular relaxation. Death takes place from paralysis either of the heart or of the respiratory centre.

Treatment.—Emetics or pump. Friction; external warmth; stimulants, such as ammonia, ether, etc.; atropine, strychnine, caffeine hypodermically. The patient if he can be roused should not be allowed to sleep.

Chronic toxic action or Chloralism—Craving for chloral is soon generated in those who are addicted to its use. Gastro-intestinal disturbance; cutaneous eruption, such as erythema, pustules, vesicles, etc.; bodily and mental weakness; sudden flushing, dyspnoea and palpitation are prominent symptoms. Death often results from an over-dose. The best treatment is the gradual withdrawal of the daily dose with generous diet, fresh air, tonics and nervine sedatives such as hyoscyamus.

Physiological antagonists.—Atropine, strychnine, physostigmine, picrotoxin.

THERAPEUTICS

Externally.—As a *local anodyne* Chloral Camphor or Chloral c. Menthol may be painted over superficial neuralgic areas, and applied within carious painful teeth. The efficacy of any of these combinations may be greatly augmented by the addition of cocaine.

Internally—As a *pure and simple hypnotic* it is unrivalled in sleeplessness due to worry, overwork or old age, but not to pain. In doses of 15 to 20 grs. it induces a refreshing sleep, which thus obtained not infrequently leads to the repeated use of the drug and thereby induces the chloral habit. It is very efficacious in febrile insomnia. In fatty degeneration of the heart a hypnotic like paraldehyde, barbitone or medinal should be used, as they do not contain any chlorine molecule. In other affections of the heart, chloral may be used safely, and is often of great value as a hypnotic. It is a most valuable remedy for *delirium tremens*. In combination with bromide of potash it will often check the

disease in the early stages. The method of administration is as follows :—During the day 20 grs. of sulphonal, dissolved in a glass of warm milk or broth should be given every 3 hours, then at 8 p.m. administer 20 grs. of chloral with 20 grs. of potassium bromide and repeat the dose every 2 hours as long as the patient remains awake. If this produces sleep, the patient may wake up perfectly cured.

Because it depresses the motor area of the cord it is extensively used in several convulsive diseases of children and adults, *viz.* eclampsia, tetanus, strychnine poisoning, hydrophobia, tetanus neonatorum, etc., specially in combination with bromides. The addition of a few drops of the tincture of Indian hemp to the chloral and bromide mixture gives very satisfactory results in tetanus.* Many other spasmodic affections, such as chorea, asthma, whooping cough, paralysis agitans, spasmodic intestinal colic are benefited by it. It is an excellent drug for lessening the rigidity of the os and other soft parts during the first stage of labour without affecting the uterine contractions.

As a *general anodyne* it is far inferior to morphine. The difference between the actions and uses of chloral hydrate and morphine is given below :—

Chloral Hydrate	Morphine
1. A quicker, and a more refreshing hypnotic.	A slower, and a less refreshing hypnotic.
2. No after-effects, such as headache, depression, and sickness (sometimes heaviness or sleepiness only).	Always headache, confusion, and narcotism.
3. No constipation. No gastrointestinal derangement in medicinal doses.	Constipation common and sometimes nausea.
4. Cannot relieve excessive pain nor induce sleep in insomnia caused by it.	Relieves pain and induces sleep in insomnia caused by it.
5. Cannot relieve reflex cough, but can relieve convulsive diseases.	Relieves reflex cough, but not so useful in convulsive diseases.

Caution.—It should be given with caution to old, gouty, rheumatic, hysterical, delicate, and otherwise constitutionally weak persons. It should not be given to confirmed drunkards, except when absolutely necessary for the treatment of delirium tremens. It is contra-indicated in threatened failure of circulation, pneumonia, acute nephritis and gastric irritation.

*R:

Pot brom.	grs. 20
Chloral. hydr	grs. 15
Tinct. cannab ind.	ms. 5
Mucilage acacia	q.s
Aqua	ad. oz. 1

Prescribing hints.—The aromatic syrup or syrup of ginger best covers its pungent taste. On account of its irritant effect it should be used freely diluted, and should not be used either in the form of tablets or pills, as when used in these concentrated forms it may irritate the stomach and the intestine. For the same reason it cannot be given hypodermically. It may be given by the rectum and is more effective than when given by the mouth. When prescribed with alkalies they decompose it and liberate chloroform, and when dissolved in alcohol it forms a poisonous compound. With camphor and menthol it forms an oily liquid and when given in solution this liquid floats.

CHLORALFORMAMIDUM (Not official) *Syn.*—Chloralamide.—Colourless, inodorous, lustrous crystals Taste, slightly bitter. *Solubility*—1 in 21 of water, freely in alcohol (90 p.c.), solution neutral to litmus

Dose—15 to 45 grs. or 1 to 3 gms.

PHARMACOLOGY AND THERAPEUTICS

Chloralamide resembles chloral in its action with this advantage, that formamide, which is a stimulant, counteracts the depression of the circulation produced by chloral alone. It is less irritant to the stomach and kidneys than chloral, but is absorbed more slowly and after absorption is converted into chloral and is excreted partly as urochloralic acid. Chloral-formamide may therefore be used as a nervous sedative wherever chloral is indicated. It takes about half to three-quarters of an hour to induce sleep, and some hold that it not only produces sleep but relieves pain. It is therefore of value in neuralgia and in relieving the pains of locomotor ataxy. Combined with bromide it has yielded good results in sea-sickness. It is incompatible with alkalies and should not be given with hot liquids.

C L U T L

Chlorbutol. $(\text{CH}_3)_2\text{C}(\text{CCl}_3).\text{OH}$

Syn.—Chloretone.

Source.—It is trichloro-*tert.*-butyl alcohol with a variable amount of water of crystallisation. Prepared by heating a mixture of acetone and chloroform with potassium hydroxide.

Characters.—Colourless crystals; odour and taste, characteristic, musty, and somewhat camphoraceous. Volatile at ordinary temperatures. *Soluble* in 125 parts of water, in 1 part of alcohol (90 p.c.), readily in ether and chloroform; in 10 parts of glycerin, and in volatile oils.

B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 gm.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Chlorbutol is an antiseptic and a mild local anæsthetic by paralysing the sensory nerve endings. An ointment with boric acid is used to soothe irritation and pain in burns and scalds, and to relieve pruritus, and an ointment or suppository (5 grs. each) is valuable in inflamed piles. Dissolved in liquid paraffin (1 p.c.) it is used as a spray in rhinitis, nasal catarrh, and sore-throat, and may be combined with menthol and camphor. Because of its antiseptic property it is used to preserve organic substances from

decomposition. In fact it is added to adrenaline chloride solution for preservation.

Internally.—The action of chlorbutol resembles that of chloral except that it does not irritate the stomach. Being a gastric sedative, small repeated doses, either alone or combined with fractional doses of calomel, act as antiemetic and check vomiting of pregnancy, sea-sickness, post-anæsthetic vomiting and vomiting of cholera.* It is a hypnotic in 10 to 15 gr. doses and is useful in nervous excitability; but is slower and less reliable than chloral hydrate. As an anti-spasmodic it is useful in hiccough, whooping cough, epilepsy and tetanus. In tetanus it may be given in 30 grs. doses dissolved in olive oil 4 grms. by rectal injection.

The usual method of administration is in powders, cachets or gelatin capsules. As it volatilises even at the ordinary temperature slowly, the powders should be dispensed enclosed in tinfoils and in stoppered bottles. When given in mixtures it should be suspended with acacia or tragacanth.

(b) Aldehyde Alcohol Group

PA AL EHY U

Paraldehyde. (Paraldehyd.). $C_6H_{12}O_3$

Source.—A product of the polymerisation of acetaldehyde.

Characters.—A clear, colourless liquid; odour strong, characteristic; taste, disagreeable. Sp. gr. 0.998 to 1.000. *Solubility.*—1 in 9 of water and with all proportions in ether, chloroform, alcohol and volatile oils.

B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

PHARMACOLOGY

Paraldehyde is readily absorbed, and manifests its action chiefly on the cerebrum, producing calm refreshing sleep, akin to natural slumber, without any after-effects or cardiac depression. It resembles alcohol in its effects, but is a more powerful narcotic and rarely induces excitement. It is therefore a pure hypnotic, but its action is more speedy, producing sleep within ten to fifteen minutes. In moderate doses, it increases the flow of urine, without deranging the digestive tract, or affecting the cardiac or respiratory centres which are paralysed only by enormous doses, death taking place from respiratory failure. It is partly eliminated by the breath, to which it imparts an unpleasant ethereal odour. A roseolous rash is sometimes noticed on the skin.

Poisoning from paraldehyde is rare. Two fatal cases have recently been recorded. In one a dose of 6 drs. proved fatal, in another

*R

Hydrarg. subchlor.	gr 1/12
Chlorbutol	gr. 1
Lactose	grs. 5

One powder every hour in vomiting of cholera or other vomiting.

a total quantity of 2 oz. taken during 36 hours proved fatal. Post mortem examination showed gastric mucosa hardened, wrinkled and greyish-white resembling the condition found in phenol or corrosive sublimate poisoning.* Two ounces given per rectum proved fatal

THERAPEUTICS

Paraldehyde may be safely used as a hypnotic in insomnia of cardiac or respiratory diseases, mania, hysterical excitement, etc. It has been tried in asylum practice and is considered to be a valuable remedy. It is used chiefly where chloral is contra-indicated, and is valuable in delirium tremens. Constant use may produce toleration of the drug.

Its action is short-lived and is useless in cases where prolonged sleep rather than speedy induction is required. A paraldehyde habit though known is of rare occurrence. Its only defect is the disagreeable taste and odour and that sometimes its use is followed by excitement and delirium.

Since it is absorbed when given by the rectum, its use has been advocated as a basal narcotic preliminary to administration of some volatile anæsthetic. It is used per rectum dissolved either in oil or in 10 p.c. solution in normal saline and is run into the rectum slowly at blood heat. It is usually given three-quarter of an hour before operation. Its action in saline is both quicker and surer than when given in oil, but its relative insolubility in the former makes the bulk of the fluid to be introduced rather large. The usual dose is 60 ms. for every stone of body weight. The solution used is paraldehyde 60 ms., normal saline $1\frac{1}{2}$ oz., glucose 5 p.c. It is a safe drug and is free from undesirable after-effects. The patient falls asleep within 30 minutes. It is also used by the same route as a sedative in mania, eclampsia, tetanus and other convulsive diseases.

It has also been used combined with ether intravenously as a general anæsthetic for short operations, $1\frac{1}{2}$ to 4 drs. with an equal amount of ether in 5 oz. of normal saline.

Prescribing hints.—Its pungent disagreeable taste may be disguised by mixing it with syrup of orange and peppermint water, or by giving in capsules. Large doses should be emulsified with compound tragacanth powder. Remember that a small dose repeated within an hour is better than a single large dose.

TRIBROMETHYL ALCOHOL. *Syn*—*Avertin*—In white crystalline powder. Contains 80 p.c. of bromine which intensifies its narcotic action. Soluble in 3 parts of water. It is dissolved in amylene hydrate (2 in 1), and 1 c.c. solution contains 1 grm. This is supplied as 'avertin liquid.'

Dose.—0.1 grm. per kilo of body weight Administered per rectum mixed with water ($2\frac{1}{2}$ to 3 p.c. solution) half an hour before commencing the operation after the rectum has been washed out the previous evening and again three hours before operation.

**British Medical Journal*, Epitome, May, 18. 1929.

ACTION AND USES

Avertin is rapidly absorbed and induces anaesthesia within 10 to 20 minutes and the patient returns to consciousness in 60 to 90 minutes after injection. It is rapidly eliminated by the urine.

It causes a fall of blood-pressure by depressing the heart and the vaso-motor system, it depresses the respiratory centre which becomes less sensitive to CO_2 , and death follows from respiratory paralysis. This is counteracted by injection of cardiac stimulants, like cardiazol.

At first avertin was used to induce general anaesthesia, but unfortunately a dose sufficient to induce anaesthesia was found unsafe and caused death from respiratory failure. Therefore it is used in smaller safe doses as a basal narcotic *per rectum* supplemented by light administration of ether or some local anaesthetic.

For rectal use the dose is 0.1 to 0.15 gm. per kilo of body weight and is administered diluted with 40 times distilled water and slowly thrown up the rectum. If an injection of hyoscine is given the patient falls asleep by the time rectal instillation is completed, when he can be removed for operation. The anaesthesia should be supplemented by ether administered by open method or by nitrous oxide and oxygen.

It is soon detoxicated by the liver where it combines with glyconic acid to form urobromic acid, in which form it is excreted by the urine. Consciousness returns within a few minutes after the administration has been completed.

It is as a rule a relatively safe anaesthetic and free from post-operative complications. It however causes some toxic changes in the liver and fatal cases of acute yellow atrophy of the liver, resembling delayed chloroform poisoning, have been described in animals after avertin. Since it increases the risk of toxic changes in the liver in chloroform anaesthesia the two drugs should not be used at the same time.

There is evidence that avertin and thyroxin are in some way antagonistic to each other, and patients suffering from toxic goitre with high basal metabolic rates feel the greatest benefit of the drug.

Contra-indications.—(1) Patients with low basal metabolic rates; they do not eliminate the drug freely; (2) abnormally low blood pressure; (3) when other drugs are used which lower blood pressure or depress the respiration, *e.g.* chloroform or morphine; (4) in operations near the rectum or anus; (5) any toxic condition; and (6) diseases of the liver and in nephritis.

Note.—Avertin is an unstable compound and should be tested before use by a few drops of 1 in 1000 solution of congo red, if no change of colour takes place then it is safe.

AMYLENE HYDRATE. *Syn.*—*Tertiary Amyl Alcohol.*—It is *Dimethyl ethyl Carbinol*. As a *hypnotic* it stands midway between paraldehyde and chloral, and is stronger than the former but weaker than the latter. In small doses it stimulates the central nervous system which is depressed in large doses, and causes a fall of temperature. It is used with avertin to counteract the depressant effect of the latter drug when used as a basal narcotic. *Dose.*—30 to 60 ms. or 2 to 4 mil.

(c) Sulphonal Group

These drugs owe their properties to the presence of Alkyl radicals (methyl, ethyl, etc.). It has been found that the introduction of the radical $\text{ethyl C}_2\text{H}_5$ into an organic compound frequently confers upon it a sedative action and these become more powerful hypnotics.

SULP ONALSulphonal. $(\text{CH}_3)_2\text{C}(\text{SO}_2 \text{C}_2\text{H}_5)_2$ **Syn**—Sulphonemethane, U S P.**Source**—It is *diethylsulphonedimethylmethane*, and obtained by the oxidation of the product of the interaction of ethyl mercaptan and acetone.**Characters**.—Colourless, prismatic crystals, or a white powder; odourless; nearly tasteless. *Soluble* in 450 parts of water, in 15 parts of boiling water; in 80 parts of alcohol (90 p.c.).**B P. Dose**.—5 to 20 grs. or 0.3 to 1.2 grms.**MET YLSULP ONAL**Methylsulphonal. $(\text{CH}_3)(\text{C}_2\text{H}_5)\text{C}(\text{SO}_2 \cdot \text{C}_2\text{H}_5)_2$ **Syn**.—Sulphonethylmethane, U.S.P. ; Diethyl-sulphone-ethylmethyl methane. "Trional."**Source**.—Obtained by the oxidation of the product of the interaction of methyl ethyl ketone and ethyl mercaptan**Characters**.—Colourless, lustrous scales, or a white powder; odourless; taste, slightly bitter. *Soluble* in 320 parts of water; in 12 parts of alcohol (90 p.c.).**B P. Dose**.—5 to 20 grs. or 0.3 to 1.2 grms.**ETHYLSULPHONAL** (*Not official*) **Syn**.—"Tetional."—Diethyl-methane-diethylsulphone Shining white, crystalline tablets, or acicular crystals with no smell but a camphoraceous bitter taste *Solubility*.—1 in 550 of water, 1 in 12 of alcohol**Dose**.—10 to 20 grs. or 0.6 to 1.2 gm.**PHARMACOLOGY AND THERAPEUTICS OF SULPHONAL AND METHYLSULPHONAL**

Sulphonal is a powerful **hypnotic** and does not depress the heart or cause the disagreeable after-effects of opium. It has no analgesic property and acts by virtue of its solubility in lipoids. It takes about four to five hours to produce sleep as its absorption is slow and uncertain. It is very useful in simple insomnia, and may safely be given in heart disease. On the other hand, it is powerless when sleeplessness is due to pain and cannot produce that soothing effect on the brain which is induced by morphine.

It is excreted slowly and may have a cumulative effect, and its prolonged administration is sometimes followed by *hæmatoporphyrin* in the urine which makes the urine cherry-red. This is more common with anæmic women and is accompanied by pain in the stomach, vomiting, weakness and ataxia, confusion, partial paralysis, suppression of urine, collapse and death. These symptoms appear several days after administration of the drug and may be after one or two weeks. There is danger of sulphonal habit. It is decomposed in the body and is found in the urine as ethyl sulphonic acid.

Although enormous doses have been taken without any ill results, its administration is not without risk when given to

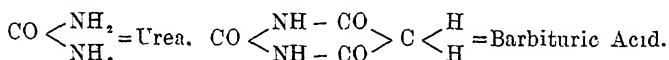
patients in a state of physical prostration, and alarming symptoms have occurred after 20 gr. doses given to patients convalescent from influenza. *Restlessness, palpitation, giddiness, and confusion of thoughts* have occasionally been observed to take the place of sleep, specially in those suffering from chronic constipation.

Methylsulphonal resembles sulphonal in its effects, but it is more prompt, inducing sleep in from 30 to 60 minutes and lasts for 8 or 10 hours. It is slightly cumulative, the toxicity appearing to increase in proportion to the increase in the ethyl groups. It has been largely used in mental diseases in which sulphonal has little or no effect. Tetronal is rarely used now.

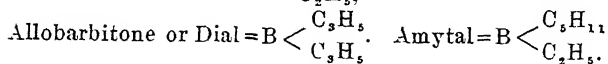
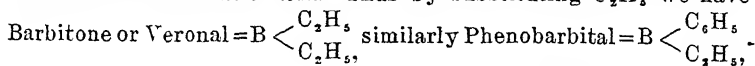
Prescribing hints.—Sulphonal may be given either in cachets or suspended in mucilage, but the best method of administration is to dissolve it in two-thirds of a tumblerful of *boiling* water, or hot soup or milk and then stir until it is cool enough to drink. It should be taken at least four hours before bedtime. When given in cachets it may remain undissolved in the stomach for hours, giving the patient no relief at night, and making him feel sleepy all the following day.

(d) Urea Derivatives

Within recent years these derivatives have assumed an important place as hypnotics, analgesics and sedatives. They are related to urea which by combining with malonic acid forms barbituric acid or malonyl urea. The relationship of barbituric acid or malonyl urea is shown in the following formulæ:—



Barbiturates are formed by substituting alkyl or aryl groups for two H atoms of barbituric acid. Thus by substituting C_2H_5 we have



B = barbituric acid nucleus and is constant.

A I T N U M

(Barbiton)

Barbitone. $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$

Syn.—Malonurea: “Veronal”; Diethyl-malonyl-urea; Barbital.

Source.—It is 5 : 5-diethylbarbituric acid, obtained by the condensation of ethyl diethylmalonate with urea.

Characters.—A white, crystalline powder. Inodorous; taste, faintly bitter. **Solubility.**—In about 170 parts of water, in alcohol (90 p.c.), in ether, in chloroform, and in aqueous solutions of alkali hydroxides and carbonates.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

A ITONUM SOLU ILE

Soluble Barbitone. (Barbiton. Solub.)

Syn.—Soluble Barbitol; "Medinal"; Veronal Sodium.

Source.—Obtained by the interaction of barbitone and sodium hydroxide. Contains not less than 97 p.c. of $C_8H_{11}O_3N_2Na$.Characters.—A white, crystalline powder; odourless; taste, bitter. *Soluble* in 6 parts of water; slightly in alcohol (90 p.c.); insoluble in ether and in chloroform.

B.P. Dose.—5 to 10 grs or 0.3 to 0.6 gm.

CA OMALUM

Carbromal. (Carbrom.)

Syn.—"Adalin"; Uradal.

Source.—Prepared by the action of *a*-bromo-*a*-ethylbutyrylbro-mide on urea.Characters.—A white, crystalline powder; almost odourless and tasteless. *Soluble* in 3000 parts of water, in 18 parts of alcohol (95 p.c.), in 14 parts of ether, and in 3 parts of chloroform.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 gm.

P ENO A IT NUM

Phenobarbitone. (Phenobarbiton.)

Syn.—Phenobarbital; "Luminal"; "Gardenal."

Source.—Obtained by the condensation of ethyl phenyl-ethylmalonate with urea.

Characters.—A white, crystalline powder; odourless; taste, slightly bitter. *Soluble* in 1000 parts of water, in alcohol (90 p.c.), in ether, in chloroform, and in solutions of alkali carbonates and hydroxidesB.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 gm.**P EN A ITONUM SOLU ILE**

Soluble Phenobarbitone. (Phenobarbiton. Solub.)

Syn.—Soluble Phenobarbital; Luminal-Sodium.

Source.—Obtained by the interaction of phenobarbitone and sodium hydroxide. Contains not less than 95 p.c. of $C_{12}H_{11}O_3N_2Na$.Characters.—A white, hygroscopic powder; odourless; taste, bitter. *Very soluble* in water, soluble in alcohol (90 p.c.). Insoluble in ether.B.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 gm.

NON-OFFICIAL PREPARATIONS

1. **Nirvanol.**—*Phenyl-ethyl-hydantoin*—A tasteless crystalline powder, slightly soluble in water *Hypnotic and sedative* Useful in *chorea* Daily dose for a child 9 to 14 years is 5 grs or 0.3 G. Treatment is followed, after one to two weeks, by pyrexia and a morbilliform rash, known as 'nirvanol sickness' when the treatment should be stopped There is oedema of the eye lids, conjunctivitis and true eosinophilia *Dose*— $2\frac{1}{2}$ to 7 grs or 0.15 to 0.45 gm.

2. **Proponal.**—*Dipropyl-Barbituric Acid*—A homologue of veronal; white crystalline powder Very narrow margin between therapeutic and toxic dose Some consider it more toxic than veronal *Dose*—2 to 8 grs or 0.12 to 0.5 gm.

3. **Bromural.** *Syn.*—*Uvaleral, Doimigene*—Colourless crystals Soluble in hot water, ether, alcohol, and the alkalis. Contains 36 p.c. bromine *Hypnotic in neurasthenia* Sleep within 5 to 25 minutes. *Dose.*—5 to 10 grs or 0.3 to 0.6 gm.

4 **Pentobarbital Sodium.** *Syn*—"Nembutal"—A white crystalline powder, freely soluble in water with a slightly bitter taste. *Dose*.— $1\frac{1}{2}$ to 3 grs or 0.1 to 0.2 gms *per os*, or per rectum. As *basal narcotic*, 3 to 5 grs or 0.2 to 0.3 gm in 10 c.c. of water intravenously.

5 **Amytal**—*Iso amyl-ethyl-barbituric acid*—A white, crystalline powder, with slightly bitter taste. Soluble in alcohol and ether, slightly in water. *Dose*.—As a *sedative*, $\frac{1}{4}$ to $\frac{3}{4}$ gr or 0.02 to 0.04 gm (*per os*); as a *hypnotic*, $1\frac{1}{2}$ to 5 grs or 0.1 to 0.3 gm., as *general anæsthetic*, 3 to 10 grs or 0.2 to 0.6 gm.

6 **Phanodorm.** *Syn*—*Cyclo-hexenylethyl Barbituric Acid*—A white, crystalline powder, with a bitter taste. *Dose*—3 grs in tablets, in mild insomnia, $1\frac{1}{2}$ grs

7 **Theominal.**—A combination of theobromine 0.3 G., and luminal 0.03 G. In *arteriosclerosis*, *angina pectoris*, and other heart affections, and climacteric disorders. *Dose*—1 to 2 tablets.

8 **Allobarbitone.** *Syn.*—*Dial, Dialyl barbituric acid*—A homologue of barbituric acid. *Dose*— $\frac{1}{2}$ to 3 grs or 0.03 to 0.18 gm

9 **Evipan.**—Methyl-cyclo-hexenyl-methyl barbiturate. A white crystalline powder, sparingly soluble in water, more freely in hot alcohol. A hypnotic. *Dose*—4 to 6 gr or 0.25 to 0.4 gm.

10. **Evipan Sodium.**—Sodium salt of evipan. Freely soluble in water. In ampoules containing 1 gm. of the powder. *Dose*—40 to 150 ms or 2.5 to 10 mls of a 10 p.c. solution intravenously.

11. **Butylethyl Barbituric Acid.** *Syn.*—*Neonal, Soneryl, Butobarbital*—A white crystalline powder. Soluble in 300 of water. Sedative and hypnotic in insomnia. Produces sleep in half an hour. Is also analgesic. Also used as basal narcotic. *Dose*—1 to 2 grs or 0.06 to 0.12 gm

12 **Pentothal Sodium.**—Yellow crystalline powder. Used intravenously to produce anesthesia in solutions of 1 gm. in 10 mls of sterile water. 3 mls generally sufficient for minor operations. For operations lasting 15 to 20 minutes one single injection is sufficient. It may be also given by repeated doses or by continuous intravenous method.

13 **Somnifaine.**—A compound of diethylamine salts of barbitone with allylisopropylbarbituric acid in glycerine-alcohol solution. Used both orally and by injection, which in urgent cases may be given by the intravenous route. Powerful *sedative* and *hypnotic*. Used with success in *mental cases* and in all conditions of excitement. Valuable in convulsive diseases like tetanus, strychnine poisoning, eclampsia, etc. *Dose*—20 to 40 drops or 8 to 16 ms (supplied in solution in drop bottles for oral use, to be taken mixed with water.) For intramuscular injection, 2 mls or one ampoule

PHARMACOLOGY OF BARBITURATES

The derivatives of this group have practically the same action, *viz* sedative and hypnotic, but differ only in degree and duration, and this depends partly upon the rate of excretion and partly upon the rate of destruction of the drug. Since barbituric acid is unstable and does not possess any narcotic action these drugs are rendered useless by the oxidation of their side-chains, and the compounds with unstable side-chains produce very short action. They all belong to the *aliphatic series*, and as such their action varies with their solubility in fats. The intensity of their action can be modified with the amount used and will produce sleep, complete insensibility or coma according to the dose. They are *analgesics*, but in this effect they are inferior to the drugs of the antipyretic group. Barbitone is a sedative and hypnotic; phenobarbitone, amyta and pernocton are more

analgesic and less hypnotic, depress the motor area, and are slightly more toxic.

Barbitone and soluble barbitone (medinal) produce refreshing sleep lasting for 6 to 8 hours without any unpleasant after-effects. They take about half an hour or more to produce sleep by their effects entirely on the central nervous system. They are about twice as active as chloral and four times as strong as sulphonal. Sometimes sleep is preceded by excitement and delirium.

Respiration and circulation.—No effect is observed on respiration, except some slowing, which is not more than found in natural sleep. Toxic doses depress the centre, when breathing becomes slower, shallower and even irregular. Death takes place from pulmonary oedema and paralysis of the centre.

Ordinary hypnotic doses have no effect on circulation. The blood-pressure remains normal though the heart may be a little quickened. Given intravenously, as for the production of anæsthesia, both the heart and the blood pressure may be depressed, the pressure however returns to normal soon.

Temperature—Sedative doses lower the temperature slightly, which becomes very low in coma due to depression of the medullary centres and also from lessened movements.

Smooth muscles.—All depress the smooth muscles producing loss of tone specially of the uterus. Amytal however has very little effect on the normal uterine contractions, and in anæsthesia produced by amytal the uterine contractions continue.

Margin of safety.—Since these drugs are extensively used as hypnotics and analgesics it is necessary that the margin of safety between the hypnotic dose and the lethal

one represented by the ratio $\frac{\text{minimum lethal dose}}{\text{minimum therapeutic dose}}$ should

be known. The higher this figure the safer the drug. Luminal is 1.3; barbitone 1.6; soneryl, nembutal and phanodorm, 2.4; dial 2.5; evipan, 5. Thus it is not very safe to give luminal in full hypnotic doses, although in sedative antiepileptic dosage it is free from immediate risk.

Absorption and excretion.—These drugs are quickly absorbed and are either decomposed or rapidly excreted by the urine. Barbitone passes out of the body in most part unchanged, about 70 p.c. being found in the urine, and takes several days to eliminate even after a single dose. Its use should not therefore be continued for more than one week, otherwise symptoms of poisoning may develop. 65 p.c. of pernocton, 30 p.c. of dial, between 10 and 40 p.c. of luminal, and no amytal could be recovered from the urine. Amytal, nembutal and evipan with unstable side chains are metab-

olised completely in a few hours. Traces have been found in the cerebro-spinal fluid and milk.

Idiosyncrasy.—In about three per cent. of cases idiosyncrasy to barbiturates is observed and toxic symptoms may arise even after administration of very small doses. They may take the following forms :—

1. *Skin* : Urticarial rashes, bullæ, morbilliform or scarlatiniform maculo-papular erythema.

2. *Gastro-intestinal* : Anorexia, nausea, epigastric pain, diarrhœa.

3. *Nervous* Defects of attention and memory, lassitude, fatigue and backache, confusion, delusions and hallucinations, diplopia, nystagmus and even coma.

4. *Circulatory* Most barbiturates are cardiac depressants of more or less serious nature, and all cause some fall of blood pressure.*

Toxicology.—The action of these derivatives varies in different individuals. While symptoms of poisoning have been reported with 1 gr. of veronal, recovery has also taken place even after 60 grs. All these drugs are more or less cumulative and the symptoms of overdosage are often due to this factor, i.e. when continued for long even in therapeutic doses, but are specially common when excretion is also scanty due to the kidneys not functioning properly. A case of delusional insanity following nembutal-ether anæsthesia has been recorded after 3 grs. (two capsules) of nembutal with $\frac{1}{16}$ gr of atropine by the mouth before administration of gas-ether anæsthesia.†

When a toxic dose is taken headache, vertigo and ataxia would appear in a few minutes, and there may be a short period of excitement. The patient would fall asleep and then pass on to coma. Babinsky's reflex may be positive for a time, but soon all reflexes and sensations are lost. Cyanosis is as a rule present with stertorous and irregular breathing which may stop for a while in the later stages. Temperature becomes subnormal, pulse rapid. Retention of urine is common. First catheter specimen contains large amount of the drug. Coma may last for several days.

Treatment.—If seen within four hours, repeated washing of the stomach with warm water. No alkalies should be given as they combine with the drug to form soluble salt which is very quickly absorbed. Put 1 pt. of strong hot coffee with some milk and 1 oz. of castor oil. If seen after six hours, lavage is still useful. In fact lavage should be repeated twice after interval of four hours. Colon should be washed out at once and again after 12 hours. Strychnine $\frac{1}{2}$ gr., picrotoxin $\frac{1}{2}$ to $\frac{1}{4}$ gr. and atropine $\frac{1}{16}$ gr. every four hours, or ephedrine 1½ grs. Subcutaneous injection of warm saline solution and rectal use of saline and glucose 4 p.c. Oxygen if cyanosis is present. Hasten removal of the poison from the central nervous system specially the vital medullary centres by lumbar puncture at once and repeated every 12 to 24 hours which helps to reduce cerebrospinal pressure and elimination of the poison.

Fatal Dose:—Death has been caused by 15 grs. of luminal and of veronal; 28 grs. of dial; and 6 grs. of nembutal used for premedication in hyperthyroidism. Average fatal dose is larger; 50 grs. for veronal, 30 grs. of luminal should be considered fatal.‡

* Castleden *The Practitioner*, Sept 1936

† *Royal Society of Medicine*, Aug. 1932

‡ E. Roche Lynch *British Medical Journal*, December, 5, 1936.

THERAPEUTICS OF BARBITURATES

The chief uses of the different preparations of this group are as hypnotics, sedatives, analgesics and anæsthetics.

As *hypnotics* these derivatives have come to the forefront and are used in preference to the sulphonal group because of their liability to poisonous effects and paraldehyde which is disagreeable. They produce almost natural sleep within 20 to 30 minutes lasting for 6 to 8 hours from which the patient wakes up refreshed, although some lassitude remains during the day. They can be used in any form of insomnia and are of extreme value when sleeplessness is due to nervous excitability, mental disease and cerebral excitement. As hypnotics, veronal and medinal are given in $7\frac{1}{2}$ gr., and luminal and amytal in $1\frac{1}{2}$ gr. doses. Luminal sodium being soluble in water can also be given hypodermically.

They are valuable *sedatives* to the brain and as such are more prompt than bromides and can be used in all cases where bromides are indicated. Of all the preparations luminal is largely used. It is also useful in vomiting of pregnancy and sea-sickness in doses of 0.06 to 0.12 grm. (1 to 2 grs.) half an hour before meals. Alone or combined with belladonna it is useful in pyloric stenosis and colic. They are all used to reduce convulsion in mania, delirium tremens, excitement following withdrawal of morphine, epilepsy, strychnine poisoning and tetanus. Because they have greater power to allay motor excitability, luminal and sodium luminal are extensively used in the convulsive diseases in preference to other drugs of this group. But their greatest field of usefulness is in epilepsy in which disease they have almost replaced bromides. In epilepsy luminal is more valuable in acute attacks and reduces both the number and severity of the fits, and does not produce that mental hebetude so common after prolonged use of bromides. The best method of administration is to prescribe $1\frac{1}{2}$ to 2 grs. twice a day, or in nocturnal attacks only one dose just before going to bed. The dose requires to be regulated, keeping in mind the idiosyncrasy of the patient and the liability of the drug to produce skin rash. It is not a cure for epilepsy and requires to be continued for a long time, possibly for years, and the dose gradually reduced. If no change is produced at the end of six months the treatment should be stopped.

As *analgesics* they are useful in headaches of all kinds, and are valuable in reducing pains of a neuralgic nature, *e.g.* sciatica, intercostal neuralgia, lumbago, dysmenorrhœa, etc. They are often used in combination with amidopyrine derivatives, *e.g.* Allonal and Veramon.

As *anæsthetics* they have been used either for the production of general anæsthesia or as a preliminary to the use

of volatile anæsthetics. Their use as a general anæsthetic by the production of narcosis is open to many objections. Being non-volatile they cannot be given by inhalation and therefore the dose cannot be regulated. If, for instance, a small dose has been given it can always be increased, but if a large dose has been introduced it cannot be withdrawn; whereas the dose of volatile anæsthetics can be regulated at will according to the need of the patient. Moreover owing to their slow excretion the narcotic effect lasts for many hours often with injurious effect to the patient. Their use therefore has not been generally accepted by many competent authorities inasmuch as the mortality following their use was greater than with volatile anæsthetics. Moreover the intravenous injections require large amounts of alkali for solution and when they enter the blood they are precipitated and remain as foreign bodies in a colloidal state, thus altering the colloidal equilibrium of the blood which may give rise to certain reflex effects. On the other hand for the production of basal narcosis as a preliminary to volatile anæsthetics they are largely used nowadays on the idea that the patient may be anæsthetised without any preliminary excitement and with a small amount of volatile anæsthetic. Unfortunately the prolonged post-operative analgesia is often accompanied by pulmonary complications resulting from prolonged respiratory depression. It is therefore necessary that preparations with short duration of action should be preferred to avoid post-operative effects which often cause anxiety. In any case it is essential when a basal narcotic is used in a combination anæsthesia, that no further narcotic of any kind should be given after operation until the patient is completely conscious and complains of pain or is very restless.

All these different drugs are not suitable for administration by one route. Evipan sodium and pentothal sodium if given intramuscularly cause severe local reaction, they are *par excellence* intravenous anæsthetics. All these drugs are detoxicated by the liver and the oxidised products are excreted by the kidneys.

The different barbiturates vary in their power of detoxication and elimination. Sodium amytal is slowly detoxicated, while evipan sodium and pentothal sodium are excreted quickly. If the property of speedy detoxication runs side by side with a wide margin of safety the drug is suitable for intravenous use in sufficient amount to produce complete narcosis and muscular relaxation. The rectal, oral, or the intramuscular route is employed for the slowly detoxicated drugs. There are however certain possible dangers which should be remembered, *viz.* (1) *idiosyncrasies* to the drug; (2) *inability on the part of the body to decompose the drug*, as happens in patients with bad liver; (3) *combination of*

several narcotics, e.g. morphine is specially dangerous and may depress the respiration profoundly.

The different preparations used as basal narcotics are :—

Pernocton—Sodium beta-bromallyl-barbituric acid. This is given intravenously about quarter of an hour before starting the inhalation anæsthesia. Resembles nembutal, but it is a more powerful hypnotic. The dose is 1 c.c. of a 10 p.c. solution per 125 kilo of body weight. Does not produce any marked fall of blood pressure like amytal. No morphine is required but atropine may be given with advantage. *Dose*.—5 grs. or 0.3 gm

Luminal is given by the mouth on the evening before operation. 10 grs. at 9 p.m. If the patient is drowsy in the morning, half the dose is given two hours before operation.

Nembutal.—Sodium ethyl-methyl-butyl barbiturate, is more sedative than hypnotic, and is less often followed by restlessness or delirium and is safer than amytal. It closely resembles amytal and produces sleep in smaller doses but more quickly. The sleep is of shorter duration due possibly to its rapid destruction in the body. For production of basal narcosis it is given intravenously ten minutes before operation. The solution should be freshly prepared and must be quite clear, and the injection given with the patient in bed, or on the operation table with a solution of $7\frac{1}{2}$ grs. in 10 c.c. at the rate of 1 c.c. per minute; the dose being the minimum amount required to put the patient into a quiet sleep. *By mouth the dose* is $1\frac{1}{2}$ to 4 grs. with morphine $\frac{1}{4}$ gr. three quarters of an hour before operation. In tetanus and strychnine poisoning give intravenously at the rate of 1 c.c. per minute of a solution of $7\frac{1}{2}$ grs. in 10 c.c.

Sodium Amytal (sodium iso-amyl-ethyl-barbiturate) is a powerful hypnotic and rapidly produces loss of consciousness and general anæsthesia. It is given intravenously in 10 p.c. solution at the rate of 1 c.c. per minute. Unconsciousness is induced very rapidly, the usual quantity required being 7 to 15 grs. It reduces the amount of ether by ten per cent. As the anæsthesia is produced very rapidly the injection is given a few minutes before operation. Owing to its effect on respiration and vaso-motor centre, it causes a great fall of blood pressure and respiratory weakness. It is however completely destroyed in the system. It is useful in strychnine poisoning when given in full doses.

Soneryl is an analgesic and hypnotic. Therapeutic doses produce no untoward effect on the circulatory or respiratory systems nor damage the kidneys. Produces sleep within half an hour and does not produce a habit.

Soneryl Sodium—Sodium derivative of butylethyl-barbituric acid. A sedative and hypnotic. Administered as a pre-anæsthetic basal narcotic in doses of $2\frac{1}{2}$ grs. per 36 pounds body weight. It is closely allied to nembutal but less toxic and has the advantage of being effective when given orally an hour before operation and atropine half an hour later. The sleep after operation is not excessive, but some patients become restless which is easily controlled by morphine. Except some depression of breathing in a few instances no other complication has been recorded.

Evipan Sodium.—It is extensively used as a non-volatile general anæsthetic. It is rapidly detoxicated by the liver, a portion remaining unchanged is excreted in the urine. It is administered intravenously; the amount contained in the ampoule (1 gm.) is dissolved in 10 c.c. of sterile distilled water just before use, as it is very unstable. The injection is made into a vein, and the patient is asked to count aloud, the rate of injection is 1 c.c. in 15 seconds, and about 3 c.c. is required to produce unconsciousness. For short operations the same amount is further added and twice as much for long operation. For elderly and debilitated patients half the amount required to produce sleep should be given.

A deep yawn just before the disappearance of consciousness, twitching of the face muscles and jactation of the limbs are common. Pupils are moderately dilated and react to light. Corneal reflex is lost during complete anaesthesia. The patient regains consciousness in ten to twenty minutes, but remains drowsy and drops off to sleep again if left undisturbed.

Contra-indications of basal intravenous anaesthesia.

1. Those having any respiratory obstruction or dyspnoea and in operations of the air passages.

2. Those whose liver is either diseased or there is impairment of its function. It is better avoided in those who are suffering from chronic kidney disease.

3. Children, because of the difficulty in giving intravenous injection and because of the small air way.

4. Those suffering from myocarditis, high blood pressure or low blood pressure.

The use of barbiturates is not always unattended with sequelae. Sometimes the patient will sleep deeply, for a period sufficiently long to cause anxiety. A minor but troublesome complication is restlessness preceding return to full consciousness. This however is less with nembutal than with others. All basal narcotics cause depression of respiratory centre, so that in some cases the breathing becomes so quiet and shallow that the patient scarcely takes sufficient anaesthetic to secure surgical anaesthesia. Cyanosis is also another complication. Toxic condition and hyperthyroidism increase the sensitiveness to these derivatives, 6 grs. of nembutal proved fatal in Graves' disease.

URETHANE. (*Not official*) *Syn.*—Ethyl Carbamate.—Prepared by the action of ammonia upon ethyl chloroformate. Colourless prismatic crystals, having a cooling saline taste; no smell. Easily soluble in water.

Dose.—1 to 2 grs. or 15 to 30 grs.

PHARMACOLOGY AND THERAPEUTICS

In *urethane* the depressing effect of ethyl on the medulla is counteracted by the stimulating effect of the carbamic radical. Thus it is free from danger to respiration and the heart even in very large doses. It is a safe hypnotic but less certain. It retards digestion but does not derange the stomach. At first it produces some excitement, but this is quickly followed by natural sleep, with some slowing of respiration and the pulse. Blood-pressure is not lowered, but large doses lower the temperature and weaken and even abolish the reflexes. It does not relieve pain. It must be given in full doses of 20 to 30 grs. which may be repeated in an hour or two if sleep does not follow the first dose. It is specially suitable for children, cases of delirium tremens, acute mania, and in the insomnia of heart disease. It is antagonistic to strychnine and has proved more useful than chloral in tetanus.

3. INORGANIC HYPNOTICS

Bromides

POTASSII I U

Potassium Bromide. (Pot. Brom.). KBr

Source.—Obtained by the interaction of ferrous bromide with potassium carbonate. Contains not less than 99 p.c. of pure potassium bromide.

Characters.—In colourless, transparent or opaque, crystals, or a white granular powder; taste, saline. *Solubility.*—1 in 2 of water, 1 in 200 of alcohol (90 p.c.).

Incompatibles.—Solution containing free chlorine or free acids, spirit of nitrous ether if acid, mercury, silver salts, and strychnine.

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm

SO II OMI UM

Sodium Bromide. (Sod. Brom.). NaBr

Source.—Prepared by the interaction of ferrous bromide and sodium carbonate. Contains not less than 99 p.c. of pure sodium bromide.

Characters.—Small, colourless transparent or opaque cubical crystals, or a white granular powder, deliquescent, inodorous; taste, saline. *Solubility*—1 in 1.5 of water, 1 in 16 of alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.

ACI UM Y MICUM ILUTU

Dilute Hydrobromic Acid. (Acid. Hydrobrom. Dil.)

Source.—Obtained by the interaction of bromine and sulphurous acid. Contains 10 p.c. w/w of HBr.

Characters.—A clear, colourless and odourless liquid. Sp. gr. 1.072 to 1.075.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

1 **Ammonii Bromidum**—In small colourless crystals, saline pungent taste. Soluble in water. *Dose*—5 to 30 grs. or 0.3 to 2 grm.

2 **Liq. Bromidi Compositus, B.P.C.** *Syn*—*Bromidia*—1 dr. contains 15 grs. of each of Chloral Hydrate and Pot. Bromide with Cannab. Ind. *Dose*— $\frac{1}{2}$ to 2 drs. or 2 to 8 mils.

3 **Bromoformum**—It is tribromomethane. Contains about 4 p.c. alcohol. A colourless, volatile, sweet liquid, with an agreeable odour. Soluble in chloroform, ether, and slightly in water. In *whooping cough*. *Dose*— $\frac{1}{2}$ to 2 ms. or 0.03 to 0.12 mil.

4 **Brometone**—*Tribrom-tertiary Butyl Alcohol*—White crystals containing about 77 p.c. bromine. Hypnotic, analgesic and antiseptic. Useful in seasickness. *Dose*—5 grs. (0.3 grm.) repeated 2 or 3 times in 24 hours.

PHARMACOLOGY OF BROMIDES

Externally.—Bromides have no action on the unbroken skin, but on the denuded surface a concentrated solution acts as an irritant.

Internally. Alimentary canal.—Either in concentrated solution applied to the throat or in repeated large doses given by the mouth, bromides diminish the sensibility and the reflex excitability of the fauces. Tickling the pharynx then no longer tends to excite vomiting even though the tactile sensation may remain. The bromides are readily absorbed by the gastro-intestinal mucous membrane and circulate as sodium bromide. Large doses in concentrated solutions produce nausea, vomiting and gastralgia by their local salt action.

Heart and circulation.—In therapeutic doses there is no essential effect on the heart and circulation, but in cardiac neurosis the bromides steady and quiet the heart's action.

through their general sedative effect. It is only when potassium bromide is used intravenously that the heart is depressed like other potassium salts.

Respiration is only slightly depressed and becomes slower. This however is not more than is observed in natural sleep. The coughing reflex is diminished.

Nervous system.—The chief action of bromides is on the entire nervous system, which is moderately depressed and owing to slow excretion this depression can be maintained for a long period without any effect on the vital centres or the medulla. This fact makes it so valuable in the treatment of epilepsy where it is necessary to keep the central nervous system depressed for a prolonged period. Used for long, even in small doses, bromides make the patient dull and apathetic with impairment of the power of concentration. They lessen the functional activity of the brain. The sensibility, excitability and emotional activity are all diminished, thereby inducing a state most favourable for sleep. They cause sleep by rendering the brain less sensitive to external influences. The sleep is not always refreshing and owing to the slow excretion is followed by drowsiness and weariness. They also depress the motor area and block the passage of sensory impulses along paths which connect the motor cells of the cord though the paths connecting cerebral centres to the motor cells of the cord remain intact. Cutaneous sensation is also impaired by comparatively small doses, not from any peripheral action but from central effect.

The vital centres are more or less depressed by large doses, and there is considerable impairment of the reflex excitability, so that larger doses of strychnine than usual are required to elicit convulsion. They diminish the irritability of the mucous membranes, the earliest and most marked being the throat which can be touched and examined without inducing reflex vomiting, although sensation of touch remains unimpaired. After large doses complete anaesthesia may be induced.

Muscles.—The bromides not only impair the activity of the muscles by their action on the motor-cells and reflex centres, but by their direct influence on the muscles themselves. They may be paralysed to such an extent that no convulsions can be produced by poisoning with strychnine. Therefore they are powerful antispasmodics.

Genitals.—Bromides decidedly lessen virility and if continued long the sexual passion, due either to its action on the brain, or diminished reflex activity.

Elimination.—In spite of the fact that elimination of bromide by the kidneys begins soon after administration, the process is slow and traces have been found 20 days after cessation of administration. Owing to this fact certain

saturation of the organism results. During a long course of bromide treatment the blood always contains bromides and the chlorides are correspondingly diminished. They also partially replace chlorides in other tissues, accumulating in the largest amounts in those organs which normally are richest in chlorine. For instance, hydrobromic acid appears in gastric juice. The elimination of bromides depends upon the amount of sodium chloride. Conversely a salt-free diet retards their excretion and helps saturation in the body. The rate of substitution depends upon the amount of bromide given, quantity of fluid and chloride intake and the efficiency of the kidneys of the patient.

As the salt intake varies in different individuals, it follows that the amount of bromide remaining in the body after a standard dose will also vary. Thus if 30 grs. of bromide be given to a person who is on low salt diet and has a small fluid intake, bromide concentration in the blood after 24 hours will be higher than when the same amount is given to a patient who is on a normal diet. This explains why some patients taking say 10 grs. three times a day develop toxic symptoms after a few weeks, while others can take the same amount for a much longer period without showing any untoward symptoms.

Bromides are eliminated by the intestinal and bronchial mucous membrane, skin, saliva and milk. Many think they depress the sensibility of the fauces during excretion.

Acute toxic action.—Acute poisoning is rare, but if $\frac{1}{2}$ to 1 oz. is swallowed, weakness, frontal headache, reduction of pulse rate, insensibility, aphasia, amnesia are the chief symptoms. Recovery as a rule takes place unless oedema of the lungs supervenes.

Barbour et al* have pointed out that the use of bromides in large doses is followed by symptoms of bromide intoxication even in the absence of so-called bromide rash. Normally the concentration of bromide in the blood is 0.5-2.5 mg. per cent. but the concentration may be as much as 500 mg. per cent. in fatal intoxication. The toxic threshold may be taken as 300 mg. per cent. Elderly patients and those suffering from arterio-sclerosis, anæmia, renal inefficiency or organic heart disease show symptoms of toxicity early and the toxic threshold with these people is in the region of 150 mg. per cent.

The symptoms of intoxication are insomnia, delirium, confusion, hallucination with varying degrees of disorientation, hysterical manifestations with torpor and death. The common physical signs are dry skin, furred tongue, tremors, blurred speech and unsteady gait.

Chronic toxic action or "Bromism."—The symptoms of chronic poisoning are observed after prolonged use of bromides, as happens in the treatment of epilepsy. The earliest of them is a rash resembling acne, which appears mostly on the face and back and sometimes may lead to boils. Mental dullness, anæmia, muscular weakness, general prostration, and dulling of cutaneous sensibility and that of the pharynx. These are followed by diminution of sexual power, and a general lowering of vitality and vigour.

In some the symptoms are more of the *psychotic type*. There may be restlessness, hallucination and delusion, disorientation and a sense of persecution. In severe cases respiration becomes depressed, slow

**British Medical Journal*, Nov. 14, 1936

and laboured, pulse feeble and eventually fever comes in followed by death.

Treatment.—As a rule stoppage of the drug is sufficient in the early stage. Administration of sodium chloride helps elimination and should be given either by the mouth in 15 gr. doses three times a day, or in urgent cases, physiological saline solution intravenously (100 to 400 c.c.) daily. Caffeine and strychnine should be given to counteract depression.

THERAPEUTICS OF BROMIDES

Internally.—Bromides are chiefly used therapeutically as sedatives in hypersensitive state of the nervous system. They are also used as hypnotics to promote sleep, but are not of value when sleeplessness is due to painful conditions. Bromides may be therapeutically used:

1. As a *hypnotic* in sleeplessness caused by worry, overwork or mental strain; but they are of no use when sleeplessness is due to pain. Sometimes however bromides fail to produce sleep and give rise to much depression and confusion. In delirium tremens, mania, acute inflammatory and febrile diseases, cerebral congestion, night screaming of children, nightmare of children and adults, bromides may be used with the greatest benefit either to induce sleep or to allay irritability. It is often combined with chloral hydrate.*

2. *To allay slight pain* which is keenly felt on account of the hypersensitiveness of the nervous system.

3. *To lessen excitability* in irritability of temper, nervous excitability of women either during the latter months of pregnancy or the change of life, hysteria, hypochondriasis, etc.†

4. *To prevent convulsions* they are used in infantile convulsions, epilepsy, puerperal eclampsia, hysteria, chorea, tetanus (p. 194), and strychnine poisoning. In epilepsy their efficacy is more marked in *grand mal*, producing little or no effect in *petit mal*. In this disease large doses are required if any physiological effects are to be obtained, and must be continued for prolonged periods. No definite results are obtained until the body is saturated with bromide, and this is helped by keeping the patient on a salt-free diet. The regulation of the dose is an important factor. Commencing with a dose of 10-15 grs. given three times a day it should be slowly increased till the maximum is reached, as judged by the patient's condition, *i.e.* cessation of fits. This dose should be maintained for some time and then reduced in the same manner. The treatment should be continued as long

*R

Pot. brom	
Chloral hyd.	aa grs. 15
Syr aurant.	ms. 30
Aqua chlorof.	ad oz 1
As a hypnotic and in convulsions.	

†R

Pot brom	grs. 10
Tinct. valer ammon.	ms. 30
Sp ether. co	ms. 15
Tinct asafetid	ms 30
Aqua camphor.	ad oz 1

as necessary, the aim being to find out the optimum dose that will keep away the fits. A few patients do not show any improvement, and in some the fits return with the stoppage of treatment. It should be noted that although other compounds may contain bromine, e.g. bromoform, they are not of any value in epilepsy since they do not liberate bromine ion in the body. Recently its use has been greatly replaced by luminal.

5. *To lessen sexual excitability*, as in chordee and nymphomania

6. As a *sedative in all spasmodic conditions*, such as pertussis, asthma, hiccough, laryngismus stridulus, etc.

7. As a *cardiac sedative* in nervous arrhythmias.

8. *To check reflex or central vomiting*, as sea sickness, etc.

9. As a *preliminary anæsthetic*, sodium bromide is used 25 to 40 minutes before operation. Twelve to 15 grm. dissolved in 25 c.c. of distilled water is introduced into a vein and the operation performed under small doses of ether to maintain full anæsthesia.

The salts most commonly used are potassium or sodium bromide, and as above mentioned it is in large and toxic doses that the potassium ion has any special depressing effect.

Potassium bromide and dilute hydrobromic acid lessen the disagreeable effects of quinine, salicin and salicylates. The usual practice is to order 2 ms. of the acid for every grain of quinine. Bromide rash is checked by keeping the skin clean and using small doses of arsenic.

Prescribing hints.—Bromides may be administered by the mouth or rectum. Their taste is fairly well disguised by the liquid extract of liquorice, milk or beer. For an enema they may be dissolved in gruel or mucilage. Their efficacy is greatly enhanced if the patient is restricted to vegetable food and a salt-free diet. The hypnotic effect of the bromides may be greatly increased if they are given with chloral hydrate, morphine or hyoscyamus. In some cases of *insomnia* bromidia may be used with great advantage. Anæmic persons cannot bear a protracted course of bromide treatment. Children, even very young ones, bear bromides well. In *whooping cough* bromoform is sometimes more beneficial than the bromides. Bromides should not be prescribed with strychnine or other alkaloids in a mixture, as they throw down alkaloidal precipitates, especially if the solution is concentrated. They should not be prescribed with mineral acids which decompose it, bromine being liberated. With organic acids no such effect is produced. Bromine is less easily formed than chlorine.

CLASS B: Drugs acting on the Cord

The cord performs three specific functions, *viz.*—(1) the conduction (a) of sensory or afferent, and (b) of motor or

efferent impressions; (2) the reflex action; and (3) the origination of impulses by special nerve centres, e.g. the sweat centres, located in the cord. The drugs acting on the cord may be divided into *spinal stimulants*, or those which increase the irritability of the anterior cornua and produce convulsions; and *spinal depressants*, or which depress or paralyse the activity of the anterior cornua.

CONVULSANTS

Drugs which stimulate the general nervous system cause exaggerated reflexes, and if the stimulation is sufficiently strong may produce convulsions, which may be *clonic* or *tonic*. Many factors contribute to the production of convulsions. Thus convulsions are observed in certain diseases due to the presence of toxins in the blood, e.g. in eclampsia, uræmia, high temperature; in irritation of the brain, as in meningitis, hæmorrhage, intracranial growth, embolism; in children due to reflex effect from some peripheral irritation, e.g. teething, constipation, worms; in neurotic conditions, hysteria, strong emotion, fright, etc.

Direct stimulation of the cerebrum is as a rule followed by convulsions of a different nature inasmuch as they are not produced by any sensory stimuli and have not a reflex character in the ordinary sense. They are irregular and only a limited group of muscles are involved and unlike strychnine no inhibition of the antagonist group of muscles takes place. The convulsions correspond to the normal co-ordinated combination of movements, *i.e.* they are *clonic* or *epileptiform*. Atropine, cocaine, santonin, produce this type of convulsion. Medullary stimulation, as from camphor and picrotoxin, also produce clonic convulsions, but these are more irregular and asymmetrical.

Convulsions induced by strychnine are spinal and reflex in character, and are due to some afferent stimulation, and affect all the muscles in a symmetrical way. They are *tetanic*, and other drugs which act like strychnine, but in a milder way are caffeine, ammonia, cocaine and thebaine.

NUX V ICA

Nux Vomica. (Nux Vom.)

Syn.—Poison-nut. Syn. I.V.—*Kuchila*, Beng., Hind.

Source.—The dried ripe seeds of *Strychnos Nux-vomica*. Contains not less than 1.2 p.c. of strychnine.

Characters.—Disc-shaped, nearly flat, sometimes irregularly bent, 10 to 30 mm. in diameter, about 4 to 6 mm. thick; rounded or somewhat acute at the margin, where there is a small prominence from which a raised line passes to the central hilum. Surface ash-grey, covered with short satiny hairs. Endosperm large, horny. Cotyledons small, leafy. Taste, intensely bitter. No odour. The *Ignatus' Beans* are the seeds of *Strychnos Ignatia*, they are olive-shaped, and contain more strychnine.

Composition—(1) *Strychnine*. 0.2 to 0.5 p.c. varying in different seeds. (2) *Brucine*, 0.5 to 1 p.c. (3) *Caffeo-tannic acid* with which strychnine and brucine are united. (3) *Loganin*, a glycoside.

OFFICIAL PREPARATIONS

1. *Nux Vomica Pulverata*. *Syn*—*Pulvis Nucis Vomice*—Nux vomica reduced to a fine powder and adjusted, if necessary, either by admixture of powdered nux vomica, or powdered lactose, to contain 1.2 p.c. strychnine. 4 grs. contain $\frac{1}{8}$ gr. of strychnine. B.P. Dose.—1 to 4 grs. or 0.06 to 0.25 grm.

2. *Extractum Nucis Vomice Siccum*.—Contains 5 p.c. of strychnine, or $\frac{1}{8}$ gr. in 1 gr. B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.

3. *Extractum Nucis Vomice Liquidum*.—Contains 1.5 p.c. of strychnine, or $\frac{1}{4}$ gr. in 3 ms. B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

4. *Tinctura Nucis Vomice*.—Contains 0.125 w/v of strychnine, or $\frac{1}{8}$ gr. in 30 ms. B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.

ST RYCHNINE HYDROCHLORIDE

(Strych. Hydrochlor.)

Strychnine Hydrochloride. $C_{21}H_{22}N_2O_2 \cdot HCl \cdot 2H_2O$

Source and characters.—It is the hydrochloride of the alkaloid strychnine. Small colourless, prismatic crystals. Efflorescent in the air, very bitter. *Solubility*, 1 in 40 of water, 1 in 80 of alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{32}$ to $\frac{1}{8}$ gr. or 0.002 to 0.008 grm.

OFFICIAL PREPARATIONS

1. *Liquor Strychnine Hydrochloridi*.—Contains 1 p.c. w/v of strychnine hydrochloride, or $\frac{1}{4}$ gr. in 12 ms. B.P. Dose.—3 to 12 ms. or 0.2 to 0.8 mil.

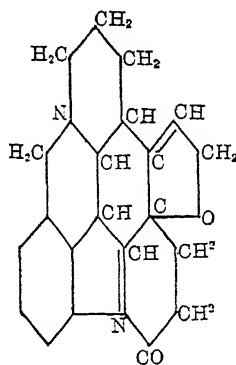
2. *Syrupus Ferri Phosphatis cum Quinina et Strychnina*. *Syn*.—*Easton's Syrup*.—1 gr. of ferrous phosphate, or $\frac{1}{2}$ gr. of iron, $\frac{1}{16}$ gr. strychnine hydrochlor. and $\frac{1}{2}$ gr. of quinine hydrochlor. in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

NON-OFFICIAL PREPARATIONS

1. *Strychnine Arsenas*.—Small, white acicular crystals, soluble 1 in 14 of water. Dose— $\frac{1}{16}$ to $\frac{1}{32}$ gr. or 0.001 to 0.004 grm.

2. *Strychnine Sulphas*, U.S.P.—Prismatic, white or colourless crystals. Soluble 1 in 35 of water. Dose, U.S.P.— $\frac{1}{32}$ gr. or 0.002 grm.

3. *Strychnine Nitras*, U.S.P.—In colourless, glistening needles, or as a white crystalline powder. Dose, U.S.P.— $\frac{1}{32}$ gr. or 0.002 grm.



Strychnine

PHARMACOLOGY

Externally.—Strychnine is a powerful antiseptic while brucine is a local anæsthetic.

Internally. **Gastro-intestinal tract**.—Being intensely bitter both nux vomica and strychnine are typical **stomachics** and **tonics**, increasing the secretion of gastric juice, and thereby sharpening appetite and promoting digestion like gentian, calumba, etc., but more powerfully. They increase the tone and peristaltic movements of the intestines by augmenting the reflex excitability of Auerbach's plexus and

may thus act as a purgative in chronic constipation due to colonic atony. For the same reason it tones up the bladder and is useful in all conditions of atony of the plain muscles. The preparations of the crude drug (dry extract or the tincture) being less easily absorbed, remain for a longer time in the intestine and act better than the alkaloid.

Blood.—Strychnine enters the blood from the mucous membrane or when given hypodermically. It is not known what effect it has on the living blood-corpuscles, though blood mixed with strychnine and shaken with air contains more oxygen and less carbonic acid.

Heart and circulation.—The heart is not affected in therapeutic doses of strychnine, but there may be some slowing of the pulse from stimulation of the vagus centre and a rise of blood-pressure from stimulation of the vaso-constrictor centres in the medulla and cord. The vessels of the splanchnic area are constricted, while those of the heart, lungs, skin (atropine effect) and central nervous system dilate. The general effect therefore is to raise the arterial pressure and allow more blood to flow through those organs necessary for the maintenance of the vital processes. This redistribution of the blood recuperates the heart by improving coronary circulation thereby supplying more oxygen and nutrition. It is doubtful if this effect is observed in therapeutic doses. It stimulates the secretion of adrenaline and thus may produce indirectly circulatory effects.

Respiration.—The medullary and spinal respiratory centres are stimulated rendering the respiration deeper and quicker. The effect is more marked when the centre is depressed by some narcotics. The respiratory muscles participate in the general tetanus and the patient dies asphyxiated from rigidity of the thoracic muscles and diaphragm.

In therapeutic doses the bronchial muscles are improved in tone, and although this may make it useful in relaxed conditions of the bronchus it will be harmful in spasmodic state of the bronchi, as in asthma. The cough centre is also stimulated.

Brain.—The higher centres are stimulated though feebly even in toxic doses and mind remains clear to the last, and the patient feels the excruciating pain of convulsion. Small doses render the special senses more acute. Thus it strengthens the mental power and sharpens the senses of sight, smell and hearing, and pain is more keenly felt. It increases the field of vision and makes the eye more sensitive to slight differences in light, due to its effects on the retinal cells and not to changes in the brain.

Medulla and cord.—Strychnine stimulates the respiratory, the vaso-motor, and to a less extent the cardiac vagal centre. But its main action is on the cord. In moderate doses it increases the tone of the muscles, *i.e.* produces

exaggerated reflexes, and makes the cord hypersensitive, so that a slight stimulus, which ordinarily causes no marked response, is followed by increased reflex excitability. In poisoning, a slight peripheral stimulus, like the prick of a pin or a flash of light or a sound, will provoke convulsions, which are sudden in onset and involve all the voluntary muscles of the body. They are at the beginning intermittent, but subsequently become tetanic, and although appear to be spontaneous are in reality always elicited by some external stimulus. The convulsions are not cerebral is shown by the fact that they can be produced in a decapitated animal. Moreover, if the posterior nerve roots are divided, or if the entire surface of the skin is anaesthetised by cocaine so that no afferent impulse can reach the spinal cord, no convulsion follows. If, however, the central ends of the cut nerves are stimulated, convulsions can be obtained. The convulsions therefore have their origin in the cord, though not initiated there inasmuch as they are reflex, being the result of afferent impulses to external stimuli.

Ordinarily when a stimulus is applied, as elicited by an ordinary simple reflex, it will not only cause contraction of one group of muscles, but by co-ordination will cause relaxation of the corresponding antagonist group of muscles (Sherrington). Thus there are two components working, one the motor and the other inhibitor. The stimulation of the flexor muscles will lead to inhibition of its antagonist the extensor muscles, and both cannot be put into action simultaneously unless the stimulus is abnormally strong. After a toxic dose of strychnine the contraction is not limited to the usual group but also involves the opposing group of muscles, *i.e.* the flexors and extensors contract simultaneously. Strychnine therefore causes a breakdown of the normal inhibitory influence and causes contraction of all the groups of muscles, and of the two sets of opposing muscles, the effect of the strongest set predominates. Therefore in case of poisoning the body becomes arched backwards (opisthotonos), the angles of the mouth are drawn back (risus sardonicus), and owing to the involvement of the diaphragm and the muscles of the chest and abdomen, the respiration becomes affected.

Nerves and muscles—Strychnine augments the capacity for muscular work and delays onset of fatigue. It has no effect on the voluntary muscles although their tone is improved through the cord. In toxic doses the functional activity of the motor nerves is depressed towards the end. This is not due to the exhaustion of the nerve tissue as has been supposed, but to the direct action of the drug on the nerves themselves.

etabolism.—The increased movements of the body naturally excite oxidation, and the absorption of oxygen and excretion of CO_2 are correspondingly increased. Owing

to increased flow of blood through the skin there is a rise in the skin temperature, but there is more heat dissipation, and any rise of temperature from increased metabolism is counteracted, and the net result is rather a fall of temperature. Glycogen in the liver and of the muscles is considerably reduced during the spasm and may disappear entirely if the spasms be of some duration. Sugar is also passed in the urine of animals experimented upon. This at one time was supposed to be a specific action, but has been proved to be due to partial asphyxia.

Genital organs.—In moderate doses, it produces sexual desire, it is therefore an aphrodisiac.

Absorption and elimination.—Strychnine is rapidly absorbed mainly from the intestine most of which is taken up by the liver where it undergoes oxidation. The rest is excreted chiefly in the urine (10 to 20 p.c.). The excretion begins within a few hours and continues usually for forty-eight to seventy-two hours, though traces may be found even after five days.

Toleration.—Some persons are more tolerant than others. Some people of India are in the habit of taking *nux vomica* morning and evening with *pan*; commencing with $\frac{1}{2}$ gr. they sometimes increase it to about 20 grs. (an entire nut).

Acute toxic action.—Within $\frac{1}{2}$ to 1 hour after a large and poisonous dose, the symptoms of poisoning commence. General uneasiness and soreness of the limbs, instantly followed by shooting pains in the back and then down the arms and legs, are first observed. Tetanic convulsions of the muscles soon set in, lasting for $\frac{1}{2}$ to 1 minute, when they relax, leaving the patient sweating and exhausted. They come on again and again, and the intermission gets shorter and shorter as the severity of the symptoms increases. The muscles of the jaw are only affected before death, not in the beginning. In short, the symptoms of poisoning closely resemble those of tetanus, from which they differ in (1) their rapid development; (2) want of a history of a wound, operation, etc., as in tetanus; (3) complete relaxation between the spasms in strychnine poisoning, whereas in tetanus the muscles of the back and jaw remain rigid between the spasms; (4) trismus or "lock-jaw" only appears as a late symptom, whereas it is the first symptom in tetanus; (5) death taking place soon, or the symptoms rapidly declining. Half a grain is the smallest dose that has been known to prove fatal.

Treatment.—Pump before convulsions, or under chloroform after convulsions. Apomorphine $\frac{1}{10}$ to $\frac{1}{2}$ gr. subcutaneously, or emetics; tannin or any preparation containing it to form insoluble tannate, which should be quickly removed before it is broken up again in the stomach. Activated charcoal adsorbs the poison, followed by potassium permanganate to destroy the same. For convulsions, use luminal sodium, amytal or nembutal, any of which may be given intravenously; large doses of bromides for prolonged effect, chloroform inhalation, artificial respiration, and oxygen, etc.

Fatal dose.—3 grs. by mouth, but only $\frac{1}{2}$ gr. if absorbed.

Methyl and Ethyl compounds of Strychnine and Brucine.—Remarkable results have been obtained by Fraser and Crum Brown when strychnine and brucine were combined with methyl and ethyl radicals. These new compounds lose their convulsant action, which they

ordinarily possess when uncombined, and produce general paralysis of the body by acting on the ends of the motor nerves like curare. In poisoning by any of these compounds, the heart continues to beat normally for a long time, and the muscles of the body remain for hours flaccid and contractile. Hence ethyl and methyl compounds of strychnine and brucine may be injected in strychnine poisoning as antidotes.

THERAPEUTICS

Internally Gastro intestinal tract.—Nux vomica and strychnine are largely used to promote appetite and digestion in **atonic dyspepsia** and **weakness of digestion** during convalescence from acute illness. Tinct. nucis vomicæ and infusion of calumba or infusion of gentian make a very efficient prescription for such cases* Strychnine has given satisfactory results in acute and chronic **gastric catarrh** and **gastralgia** ($\frac{1}{100}$ gr. hypodermically). Because it increases peristalsis, nux vomica is frequently given as an adjunct to purgatives. It is a valuable remedy in chronic constipation without the aid of other remedies

Heart and circulation.—As a circulatory stimulant its value is doubted by many. The chief use of strychnine is in cases of pure failure of circulation due to vascular paralysis leading to collapse. It has no effect when the circulatory failure is a capillary stasis, or when the vessel walls have lost their excitability. To get any improvement the dose should be $\frac{1}{10}$ to $\frac{1}{2}$ gr hypodermically (Gunn)

Respiration.—As it stimulates the cough centre, it helps expectoration by provoking coughing, and is useful in chronic bronchitis, protracted pneumonia, etc., when given with other expectorants. It averts death in chloroform poisoning ($\frac{1}{30}$ gr. hypodermically). As a respiratory stimulant it is valuable during anæsthesia, surgical shock, poisoning by opium, chloral, etc., and in exhaustion of the centre, as in **pneumonia**. In these conditions improved respiration will result in increased supply of oxygen to the heart and central nervous system, and there will be a break in the vicious circle thus enabling the patient to maintain the effect even after the stoppage of the drug. In these cases it should be given in full doses when it may tide over a critical period.

Nervous system.—As a spinal stimulant strychnine is used in diseases of the nervous system, but the conditions in which it can be of service are very limited, and its use requires careful discrimination. It is useful in (a) *paresis* or incomplete paralysis; (b) *local paralysis* as that of the forearm, larynx, sphincter, etc., due to any toxic agent, as lead,

*R:

Acid hydrochlor. dil.	ms 10
Tinct nuc vom.	ms 10
Sp. chloroform	ms 15
Inf gentian co. rec.	ad oz 1

alcohol, or tobacco; (b) *diphtheritic paralysis*; and (d) *post-operative paralysis* of stomach or intestine. Its use has been suggested in infantile paralysis, but since there is destruction of the anterior cells of the cord the use of strychnine can have no influence in restoring the destroyed nerve cells. Indeed if used early it may be positively harmful by irritating the surrounding area of inflammation. Similarly its use in lesions of the motor area of the brain, or of the motor tract of the brain and cord can only be harmful. It should not be used (a) when the paralysis is of recent origin; (b) when rigidity of muscles still exists; (c) when there is much wasting of muscles (sometimes progressive muscular atrophy is stayed in its progress by the hypodermic injection of $\frac{1}{80}$ gr. increasing to $\frac{1}{40}$ gr given once daily); (d) when head symptoms are present; and (e) when the muscles do not respond to electricity.

Besides the above, *nux vomica* or strychnine can be successfully employed in atonic conditions of the bladder and sexual debility. In mental depressions from overwork it should be used after the suspension of work.

Prescribing hints.—The effect of strychnine depends upon its rapidity of absorption. Given hypodermically it is two to eight times stronger than when given by the mouth. When administered per rectum the effects approach more closely the hypodermic method. Children are comparatively insusceptible to it. Toleration is not induced, on the other hand, long continued use renders the nervous system more sensitive to it.

CLASS C: Drugs acting on the Sympathetic and Parasympathetic Nervous Systems

The voluntary muscles are under the direct control of the central nervous system, but the activity of the involuntary muscles and of the glands is regulated by a more complex arrangement. A characteristic feature of these involuntary active organs is that they can work independently of the central nervous system and for this reason their nervous system is known as *autonomic system*, although this is also influenced in all its parts by the centres. The nerves supplying them do not pass directly from the central nervous system, but medullated fibres are projected from the cord and run to ganglion cells whence non-medullated fibres pass down to the different tissues. The autonomic system has been classified into (1) *cranial autonomic*, (2) *sympathetic proper*; and (3) *sacral autonomic*. The cranial and sacral autonomic systems have complementary physiological functions and are known as *parasympathetic system*.

The *sympathetic system proper* consists of a chain of ganglia or collections of nerve cells situated on each side of the vertebral column. The "outflows" from the sympathetic arise from the dorsal and down to the fourth and fifth lumbar nerves as minute medullated fibres. These have their cell stations in the ganglia of the sympathetic cord, and in the cardiac, solar and hypogastric plexuses.

The "outflows" from the *parasympathetic* include the cranio-bulbar and the sacral outflows. The cranial group is formed by the third, the seventh, the ninth and the tenth; while the sacral group

by the second, the third and the fourth sacral nerves. The parasympathetic fibres which run into the oculo-motor arise from the mid-brain and supply the ciliary muscle and the iris. The seventh and the ninth emerge from mid-brain and supply the vaso-dilators and the secreting glands in the nose, the mouth and the pharynx. The chorda tympani becomes bound up with the branches of the 5th and is distributed with them. Finally from the mid-brain emerge the vagi which supply the heart, the bronchial muscles, the oesophagus, the stomach and the small intestine, and also regulate the secretory mechanism. The fibres from the sacral region supply the vaso-dilators, the external generative organs, the bladder, the rectum, the anus, and motor fibres to the musculature of the descending colon and rectum. It will be seen that the autonomic fibres arise only from certain sections and not in an unbroken succession from the central organs, and act as conducting paths to carry impulses from the central nervous system to the different internal organs, and by means of their endings either augment or depress their functions. All the functions of these organs are performed even if the organs concerned are separated from the control of the central nervous system. The brain however influences their activity, and even psychical stimulation, *e.g.* fright, excitement or emotion, is followed by changes in the activity of the heart (acceleration), vessels (flushing), and even of different secretions (sweat).

The sympathetic and the parasympathetic systems are antagonistic to each other both physiologically and frequently pharmacologically. In most organs where the two types of nerve influences act, they affect their functions in opposite directions, *i.e.* they lead to opposite results. Thus the pupil is contracted by the parasympathetic fibres running along the third nerve, while it is dilated by the sympathetic supplying the dilator pupillæ. Similarly, the parasympathetic vagus inhibits the heart, while the sympathetic accelerates it. It must not be supposed that the sympathetic alone is concerned with augmentation and the parasympathetic with inhibition. Though the vagus is the inhibitor nerve of the heart, it is the motor to the bronchial muscle. Similarly the sympathetic is inhibitory to the intestine and the coronary arteries. Some organs are innervated by one division only, *e.g.* the uterus and most arterioles are supplied by the sympathetic only, while the glands of stomach and pancreas by parasympathetic only.

The exact manner in which drugs influence the autonomic system was till lately obscure. Since the effects of some drugs resemble those following either stimulation or depression of the sympathetic or the parasympathetic systems, attempts have been made to explain their action as being due to their effects on the nerve-endings. In fact they act on an organ whose nerves have been divided and have degenerated and in which no nerve terminations exist. In view of the fact that nerve fibres are not influenced by most of the specific autonomic drugs, it is doubtful that the finer terminal fibrils, which are continuations of the axis cylinders, should be the seat of action of these drugs. Their action therefore must be exerted on some substance beyond the termini of the nerves. It has therefore been suggested that they act on the muscle cells directly, a fact rather difficult to reconcile, inasmuch as some drugs, notably adrenaline, act differently on different involuntary muscles in spite of the fact that they react uniformly to other stimuli. The natural conclusion out of this controversy is the assumption that there exists some intermediate structure between the nerve-endings and the muscle, which has been differently named as "receptor substance," "myoneural junction" or "synapse." This theory even has been challenged on the ground that pilocarpine which stimulates the secretion of sweat and choline which causes contraction of the striped muscles

are both antagonised by atropine, although there is no evidence of parasympathetic nerve-endings in these structures.

Dixon pointed out that after stimulation of the vagus nerve to the heart a substance could be extracted from the heart muscle which was inhibitory in its action on other hearts, and which effect could be antagonised by atropine, just as it antagonises vagus stimulation. This work was subsequently revived by Dale and Loewi, who have pointed out that these drugs act not by stimulating the nerve-endings but by liberation of certain chemical substances, *e.g.* acetyl-choline, or adrenaline-like substance termed *sympathin*. It has now been demonstrated that the nervous impulse is transmitted from the post-ganglionic fibres through the autonomic ganglia. The sympathetic post-ganglionic fibres liberate at their ends substances which act physiologically like adrenaline and similarly the parasympathetic post-ganglionic fibres liberate acetyl-choline at their terminals. Whereas all the pre-ganglionic fibres (whether they belong to the sympathetic or the parasympathetic system) liberate acetyl-choline at their ganglia (excitor neurones), and this substance probably stimulates the excitor cells to discharge a fresh group of nervous impulses. Drugs which stimulate the sympathetic act not because of the physical stimulation but by the formation of sympathetic hormone, adrenaline, around the cell. Similarly those stimulating the parasympathetic act by the formation of the hormone, acetyl-choline. Dale suggested that nerve fibres which liberate at their terminals, bodies resembling adrenaline or acetyl-choline, should be called "adrenergic" or "cholinergic." Adrenergic fibres are therefore only present in the post-ganglionic fibres of the sympathetic, but the cholinergic fibres include the post-ganglionic fibres of parasympathetic system and all the pre-ganglionic fibres of both the sympathetic and parasympathetic systems.

Certain post-ganglionic fibres anatomically belonging to the sympathetic system (sympathetic supply to the sweat glands) act like parasympathetic by liberating acetyl-choline. In other words they are cholinergic and functionally should be regarded as part of the parasympathetic system.

According to this theory atropine and ergotoxine act directly on the cells and render the tissues insensitive to acetyl-choline or adrenaline, thus preventing the effects of parasympathetic or sympathetic stimulation. Pilocarpine, as is known, contracts the pupil after the degeneration of the 3rd nerve but not physostigmine. It has therefore been suggested that physostigmine prevents the action of the ferment choline esterase which normally destroys acetyl-choline and therefore does not act on the denervated organs in which no acetyl-choline is liberated.

The result of sympathetic and parasympathetic stimulation on the different organs is set out in the following table. But it should be remembered that the function of certain nerves is still uncertain.

The effects of Sympathetic and Parasympathetic stimulation on different organs.

Organ	Sympathetic	Parasympathetic
Eye	Pupil: Dilatation from stimulation of the radiating fibres. Ciliary ms.: relaxation.	Pupil: contraction from stimulation of circular fibres. Ciliary ms.: contraction.
Bronchioles	Muscles: relaxation. Glands: nil.	Muscles: contraction. Glands: increased secretion.

Organ	Sympathetic	Parasympathetic
Alimentary canal	Relaxation, except the sphincters which contract. Secretion: inhibition.	Augmentation of peristalsis except the sphincters which relax. Secretion: increased.
Heart	Acceleration of rate.	Slowing of rate.
Arterioles	Constriction, except coronary vs which dilate.	Nil as a rule.
Uterus	Mixed effect. Excitation or inhibition depending on the preponderance of particular nerves whether motor or inhibitory.	Nil.
Bladder	Relaxation, except the sphincter which contracts.	Contraction, except the sphincter which relaxes.
Salivary glands	Slight viscid secretion.	Increased secretion and vaso-dilatation.
Sweat glands	Though supplied by sympathetic they act as if they are supplied by parasympathetic. Therefore perspiration is induced by parasympathetic stimulants and inhibited by parasympathetic depressants, i.e. the fibres are cholinergic.	

Drugs acting on the sympathetic system.—The sympathetic fibres have two actions, *augmentor* and *inhibitor*. The augmentor effects are acceleration of the heart, vaso-constriction, dilatation of the pupil, increased secretion of saliva, tears, etc. The inhibitory effects are chiefly confined to the stomach, intestine, gall-bladder, bronchi, and the urinary bladder. It has also an inhibitory effect on the virgin uterus of cat.

(a) *Drugs which stimulate the sympathetic endings.*—Adrenaline, ephedrine, tyramine, and ergotoxine in small doses. Cocaine increases the peripheral excitability without directly stimulating it.

(b) *Drugs paralysing the sympathetic nerve-endings.*—Ergotoxine in large doses paralyses the motor fibres of sympathetic, ergotamine and apocodeine.

Drugs acting on the parasympathetic system.—With the exception of vagus this system is mainly augmentory. Parasympathetic stimulation causes slowing of the heart, contraction of the pupil, spasm of the bronchial muscles, increased secretion of all glands centrally innervated, viz., sweat, saliva, stomach and contraction of the intestines, uterus and most plain muscles. The urine, secretion of bile, milk and the internal secretions are not affected by this system.

(a) *Drugs stimulating the parasympathetic endings.*—Muscarine, pilocarpine, physostigmine, acetyl-choline and anaphylotoxin

(b) *Drugs depressing the parasympathetic endings.*—Atropine, hyoscyamine, hyoscine. They produce results opposite to stimulation.

DRUGS ACTING ON THE EYE

Drugs acting on the pupil.—The iris is the regulator of the pupil. It is composed of two sets of fibres, the circular which contract.

and the radiating which dilate. These sets of muscles are in constant action, and by opposing each other constitute a sensitive balanced mechanism for the regulation of the size of the pupil. The sphincter iridis (circular fibres) is supplied by the 3rd or oculo-motor, which arise from the mid-brain, and the centre for the contraction of the pupil is located in the corpora quadrigemina. Stimulation of the 3rd nerve contracts, and its section dilates the pupil. The cervical sympathetic is the nerve for the radiating fibres; its stimulation causes dilatation and its division, contraction of the pupil. The oculo-motor centre is kept under control by impulses passing from higher centres, and if these higher centres are inhibited, as during sleep, during surgical anaesthesia and in opium poisoning there is contraction of the pupil (Mayer and Gottlieb).

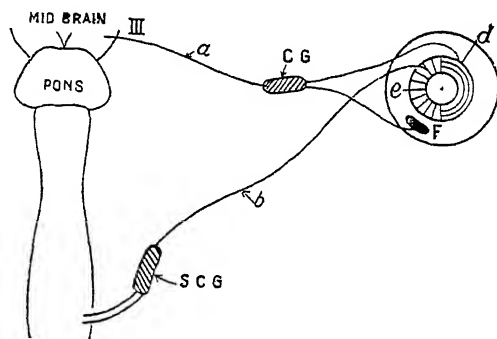


Fig 3.—Explaining Action of Drugs on the Pupil III—3rd nerve showing the pre-ganglionic parts and the endings supplying the circular fibres of the iris (d) and the ciliary muscle (F) S C G, superior cervical ganglion and sympathetic (b) supplying the radiating fibres of the iris (e)

Mydriatics or pupil dilators act as follows:—

1. *By paralysing the oculo-motor nerve-endings*, as atropine, hyoscine, homatropine, conine, gelsemine.
2. *By stimulating the endings of the cervical sympathetic*, as cocaine, tyramine, adrenaline and ephedrine.
3. *By depressing the oculo-motor centre*, as in asphyxia (general anaesthetics, fourth stage).

Strong emotion, fear, excitement and asphyxia dilate the pupil either by stimulating some centres of the sympathetic nerve supplying the eye and simultaneous inhibition of the oculo-motor centre, or by stimulating the sympathetic supply of the adrenal gland and causing an increased secretion of adrenaline.

Myotics or pupil contractors act as follows:—

1. *By stimulating the endings of the third nerve*, as choline, pilocarpine, physostigmine, nicotine, muscarine.
2. *By stimulating the centre for contraction*, as opium, picrotoxin, general anaesthetics in the early stage. For action of opium, see *supra*. Nicotine, conine and lobeline first stimulate and then depress the ganglion cells of both the oculo-motor nerves, therefore the pupils first contract then dilate.

Drugs that impair accommodation.—Ciliary muscle adjusts the lens for distant and near objects of vision. During rest, the lens remains flattened, but to see near objects it becomes more convex owing to the drawing in of the ciliary processes by the contraction of the circular fibres. It is supplied by the 3rd nerve. Drugs that paralyse accommodation by acting on the ciliary muscle are called *cycloplegic*, they are atropine, gelsemine, pilocarpine, physostigmine.

Drugs affecting the intra-ocular tension.—The normal tension depends upon (a) the amount of intra-ocular secretion, (b) the freedom with which fluids may escape through the lymph channels (spaces of Fontana) into the canal of Schlemm. Tension may be raised by extra secretion or by dilatation of the pupil which shuts off the spaces of Fontana.

1. *Drugs increasing the tension*, atropine, hyoscine and hyoscyamine
2. *Drugs decreasing the tension*, pilocarpine and physostigmine.

1. Drugs Stimulating the Parasympathetic endings

Muscarine, an alkaloid derived from poisonous mushroom, *Amanita muscaria*, has the same pharmacological action as pilocarpine except that it produces more nausea and vomiting. It is not used therapeutically.

PILOCA PINAE NIT AS

(Pilocarp. Nit.)

Pilocarpine Nitrate. $C_{11}H_{16}N_2O_2 \cdot HNO_3$

Source and characters—The nitrate of an alkaloid, pilocarpine, obtained from the leaves of *Pilocarpus microphyllus* and other species of *Pilocarpus*; in colourless crystals, or white crystalline powder. Soluble in 8 parts of cold water.

B.P. Dose.— $\frac{1}{10}$ to $\frac{1}{8}$ gr. or 0.003 to 0.012 gm.

NON-OFFICIAL PREPARATIONS

- 1 **Guttæ Pilocarpinæ.**—Pilocarpine Nitrate 0.5 to 1 p c.
- 2 **Pilocarpine Hair Lotion.**—Pilocarpine Nitrate 2 grs, Quinine Hydrochloride 8 grs, Glycerin 2 dis, Aqua Rose 6 dis.

PHARMACOLOGY

Pilocarpine is directly antagonistic to atropine in its effects upon the secretory nerves, the ends of the nerves governing the involuntary muscles, the ends of the vagus, and the ends of the third nerve in the eye. These effects are due to parasympathetic stimulation and will act even after the nerves are divided and allowed to degenerate.

Internally.—Pilocarpine readily enters the circulation and is carried to different structures, where it produces definite effects, which are described below under separate heads:—

Salivary secretion.—Within about ten minutes after administration, pilocarpine produces a copious secretion of saliva of almost normal composition by directly stimulating the parasympathetic (cholinergic) nerve-endings of the chorda tympani and the glosso-pharyngeal endings in the glands. It is therefore a powerful sialagogue, the secretion amounting to a pint and a half, after one injection. The salivation is immediately stopped by injection of atropine.

Stomach and intestine—The peristaltic movements of the unstriped muscles of the gastro-intestinal canal are increased by large doses owing to direct stimulation of the parasympathetic endings of the vagus, causing nausea, vomit-

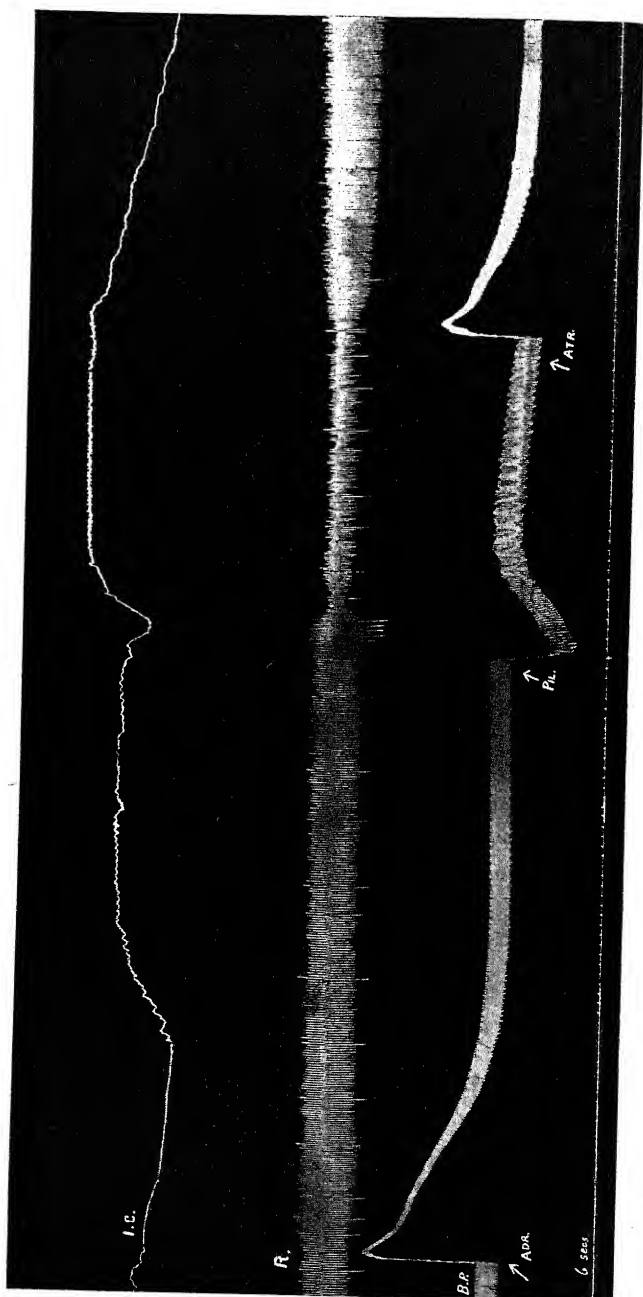


Fig. 4.—Dog. Showing effect of Adrenaline, Pilocarpine and Atropine on blood-pressure, respiration and intestinal contraction.

Note the rise of blood-pressure and relaxation of the intestine, with adrenaline; fall of pressure, spasm of bronchial muscles and increased intestinal contraction with pilocarpine. All these effects are antagonised by atropine, i.e. it causes rise of pressure, relaxation of the bronchial muscles and of the intestine.

ing, colicky pain and diarrhœa. The pancreatic secretion is slightly affected, possibly due to muscular contraction of the duct, or indirectly through increased gastric secretion. The gastric juice and intestinal secretion are also increased. The biliary secretion is unaffected, but the spleen contracts.

Skin—The next important action is on the skin. Within six to ten minutes after a hypodermic injection of pilocarpine nitrate ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) the face, neck and ears become flushed and drops of perspiration appear upon them, soon extending over the whole surface. The sweating is so profuse as to soak garments and bed clothes; about 2 to 3 litres of sweat may thus be excreted by one diaphoresis. Therefore it is a powerful sudorific. The sweating is checked by atropine. Although the sweat glands are innervated by the sympathetic fibres, these functionally act as parasympathetic and are cholinergic in their effects so that pilocarpine causes increase of perspiration by stimulating these fibres. It also stimulates the growth of hair, and makes it coarse and black.

Circulatory system.—Both the heart and pulse are accelerated at first, but are soon slowed and depressed. Quickening is the usual therapeutic effect when pilocarpine is given by the mouth. It excites both the vagal and sympathetic endings, and when given by the mouth the drug reaches the heart slowly and the sympathetic effect predominates; whereas when a large dose is given directly into the circulation the vagal effect becomes marked and the heart is slowed. Atropine counteracts the slowing of the pulse, but it cannot do so if the vagus is cut; thus showing that pilocarpine depresses the heart by stimulating parasympathetic endings of the vagus. It also depresses the heart directly, therefore the margin of safety is small, and its use has been followed by collapse and death. The vessels of the body specially those of head and neck dilate and the blood-pressure falls from depression of the vaso-constrictor centre and the heart, though there may be a rise at first from vasoconstriction due to some liberation of adrenaline and contraction of the vessels of the splanchnic area. In toxic doses there is vaso-motor paralysis.

The number of white blood corpuscles (lymphocytes) is increased from contraction of the spleen muscles.

Respiratory system.—Pilocarpine increases both the nasal and bronchial secretions, and owing to the increased contraction of the bronchial muscles the breathing may be laboured and the amount of air entering and leaving the lungs is diminished. The respiratory centre is not affected directly by small quantities of pilocarpine, but the circulatory changes diminish the amount of blood passing through the lungs. These effects combined with circulatory depres-

sion tend to promote cedema of the lungs, asphyxia, collapse and death.

Eyes. (a) *Pupil*.—Locally applied or given by the mouth or subcutaneously, it causes contraction of the pupil. This effect, which is prevented by the previous use of atropine, is due to stimulation of the myoneural junctions of the oculomotor nerve, and observed even after the nerves have degenerated. There is no stimulation of the sphincter muscle itself. It increases the flow of tears.

(b) *Accommodation*.—The ends of the third nerve in the ciliary muscle are stimulated, causing bulging of the lens and fixation of the eye in accommodation for near objects.

(c) *Intra-ocular tension*.—After a momentary rise the tension is diminished. This coincides with the contraction of the pupil and results from the increased escape of fluids which follow the opening of the spaces of Fontana.

Urinary tract.—Pilocarpine has no effect on the secretion of the urine, in fact the great loss of fluid by other channels causes a decrease in the amount of urine. Large doses given repeatedly produce glycosuria and diuresis probably by increasing the renal permeability. By its contractile effect on the bladder it causes suprapubic pain and irresistible desire to pass water.

Body heat and weight.—On account of the dilatation of the cutaneous vessels before sweating, there is a slight rise of temperature, but it soon falls during sweating. There is also a reduction of body weight to the extent of seven pounds or more.

Female generative organs.—Pilocarpine causes the uterine muscles to contract, sometimes to such an extent as to cause abortion. It also increases uterine and vaginal mucus. The secretion of milk is not affected, although earlier investigators claimed for it a galactagogue action. It is evident that the mammary glands do not possess any true secretory nerves.

Summary of action —It will be observed that pilocarpine performs two most important specific functions, viz. :—(1) *Stimulation of secretion*, (2) *contraction of the involuntary muscular fibres* due to stimulation of the nerve-endings and not to that of the muscular fibres themselves. *Salivation*, *diaphoresis* and *myosis* are the most marked effects. Children are less affected than adults.

Antagonists —Belladonna and atropine. $\frac{1}{150}$ gr. of atropine given subcutaneously arrests profuse salivation and diaphoresis within 5 to 10 minutes.

THERAPEUTICS

Externally—To promote the growth of hair, pilocarpine is largely employed in the form of hair lotion. In ophthalmic

practice, it has been locally applied in iritis, retinitis, detachment of the retina, glaucoma, etc., but it is less active than physostigmine, and its effects more transitory.

Internally—Pilocarpine is chiefly employed for its diaphoretic action in uræmia and uræmic convulsions, where it may be the means of saving life by the elimination of excretory products through perspiration. It is however now recognised that in uræmia poisons other than urea are responsible for the untoward symptoms, and the beneficial effect is due more to the improvement of circulation following removal of fluid which impairs kidney circulation, than to the elimination of the poison *via* the skin. It is of special service in nephritis. Under these conditions it promotes perspiration and secures functional rest to the kidneys and lowers blood-pressure. When there are anasarca and serous effusions, $\frac{1}{8}$ to $\frac{1}{2}$ gr. pilocarpine nitrate produces profuse sweating and salivation, thereby relieving the waterlogged system which in its turn will cause an improvement in the kidney circulation resulting in its recovery. In cardiac dropsy it should be used with caution. Its use is often followed by weakness, languor, and general depression which may counterbalance any improvement following its use. The diaphoresis can be helped by wrapping the patient in warm blankets and giving him warm drinks. For its antagonistic properties it is used in poisoning by belladonna.

Caution.—Sometimes alarming prostration and collapse may follow the hypodermic injection of $\frac{1}{4}$ gr.; and atropine should at once be injected. It should be used with great caution in valvular diseases of the heart, fatty heart, emphysema and pleurisy, and the patient watched. It is contraindicated in renal diseases associated with cedematous condition of the lungs, as by increasing bronchial secretion it may add to respiratory distress. Children are less affected than adults.

PHYSOSTIGMINE SALICYLATE

(Physostig Salicyl.)

Physostigmine Salicylate. $C_{15}H_{21}O_2N_3$, $C_7H_6O_3$

Syn.—Eserine Salicylate.

Source.—The salicylate of an alkaloid, physostigmine, obtained from the seeds of *Physostigma venenosum*.

Characters.—Colourless, or faintly yellow, crystals, gradually acquiring a red tint on exposure to light and air. *Soluble* in about 100 parts of water, freely in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{100}$ to $\frac{1}{2}$ gr. or 0.0006 to 0.0012 grm.

OFFICIAL PREPARATIONS

1. **Lamella Physostigminæ.**—Contains $\frac{1}{1000}$ gr. (0.065 mg.) of physostigmine salicylate in each.

2. **Oculentum Physostigminæ.** *Syn.*—*Oculentum Eserinæ*—Contains 0.125 p.c.

PHARMACOLOGY

The action of physostigmine resembles pilocarpine and though like pilocarpine it stimulates the cholinergic fibres, its effects are not so marked on the secretory glands; on the other hand its action on the involuntary muscles is more marked. Its action however is different from pilocarpine and it will not act after the nerve has been cut and degenerated. Since acetyl-choline which is liberated at the nerve terminals is rapidly hydrolysed, it has been suggested that physostigmine prevents this destruction by the ferment choline-esterase in the blood and tissues. It is however not definitely settled whether all the actions of physostigmine are due to this effect or it has some direct action on the involuntary muscles.

Eye.—Applied locally to the conjunctiva, physostigmine is absorbed and produces the following changes—(1) **contraction of the pupil**; (2) **accommodation** for near objects due to the contraction of the ciliary muscle; (3) **diminished intra-ocular tension** due to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana. All these actions are due to the *direct stimulation of the parasympathetic endings of the third nerve.*

Physostigmine fails to produce contraction of the pupil after degeneration of the third nerve, although the muscle of the iris is intact and can be made to respond to electrical stimulation or other drugs. This is due to the fact that physostigmine inhibits the activity of the ferment choline-esterase which normally destroys acetyl-choline.

Internally Mouth.—Physostigmine increases the **salivary secretion** by stimulating the endings of the chorda tympani. The effect is not central as the secretion can be induced after section of the nerves, and since the secretion is not checked after administration of nicotine, salivation cannot be from any action on the ganglion cells, which are paralysed by nicotine. But if the nerves are paralysed by the previous use of atropine it fails to produce any secretion.

Stomach and intestines.—It is readily absorbed by the stomach and increases the gastric and intestinal movements by stimulating the vagal endings. In therapeutic doses the peristaltic movements become more active, consequently there may be vomiting, and since the intestinal contents are hurried down, there is diarrhoea with watery stools.

Heart and circulation.—In small doses it increases the contractile force of the heart, causing slowing of the pulse and rise of blood-pressure. In large doses the slowness is increased although the blood-pressure falls. This action is due to stimulation of the vagal endings in the heart. In frog it stimulates the heart directly.

The blood-pressure rises from the increased contractile force of the heart aided partly by (a) the contraction of the arteries by the direct stimulation of the arterial nerve endings, and partly by (b) the tetanic contraction of the intestinal tract thus expelling the blood from the mesenteric area. It is therefore independent of the vaso-motor centre, for its action is not prevented by section of the cord or of the splanchnic nerves.

Respiration.—This is at first quickened but soon depressed. The acceleration is caused (1) by the stimulation of the respiratory centre of both the medulla and the cord ; (2) by the stimulation of the peripheral terminations of the vagus in the lungs ; and (3) by the spasmodic contraction of bronchial tubes producing partial asphyxia. Death takes place from failure of the respiratory centre.

Nervous system—The motor cerebral cortex becomes • more excitable causing epileptiform convulsions ; these have been attributed to partial asphyxia caused by respiratory paralysis and bronchial constriction. In large doses it depresses the central nervous system beginning from the cord and spreading upwards with diminished reflex excitability. The consciousness is not affected even by toxic doses, and the mind remains clear to the last. The pupils may be contracted, but not as a rule to any great extent. The respiratory centre is stimulated first as mentioned before.

Muscles.—Marked fibrillary contraction of the voluntary muscles is often seen. This is due to the stimulation of nerve-endings of the striated muscles for it takes place when the nerves have been divided, but disappears if the motor nerve-endings are paralysed by curare but not by atropine and does not occur after the nerve ends have degenerated. It has therefore been suggested that it acts on the motor end-plates of the voluntary muscle. The sensory nerves remain unaffected. The involuntary muscles of almost every organ such as the stomach, intestines, bronchioles, bladder, heart, arteries, spleen, uterus, iris, etc., are stimulated producing powerful contraction.

Secretions—Not only saliva, but sweat, tears and buccal mucus are increased in much the same way as with pilocarpine but the action is not so powerful. The secretion of adrenaline is also increased. The secretion of milk, bile and urine is not affected.

Elimination.—Physostigmine is excreted by the liver and salivary glands, not by the kidneys.

Antagonists.—Atropine, chloral, strychnine and morphine

Toxicology—Poisoning by physostigmine is rare. Emetics or pump. Stomach wash with 0.2 p.c. potassium permanganate. Atropine $\frac{1}{16}$ gr hypodermically till the pupils dilate well. Strychnine if necessary. Artificial respiration overcomes respiratory trouble.

THERAPEUTICS

Eye.—Eserine is chiefly used (1) to contract the pupil in photophobia, and diminish the amount of light falling on a sensitive retina; (2) to break up adhesions in iritis; (3) to prevent prolapse of the iris after corneal wounds, ulcers or perforation; (4) to reduce intra-ocular tension in glaucoma and perforating keratitis; (5) to stimulate the paralysed ciliary muscles and iris; (6) in detachment of the retina; and (7) to antagonise the effects of atropine, homatropine and cocaine on the pupil. It is generally used in $\frac{1}{2}$ to 1 p.c. solution, 2 to 4 drops being dropped into the eye at a time.

For its depressing effect on the central nervous system it has been used in several convulsive diseases, chiefly tetanus, chorea, etc., but without any appreciable benefit. As it increases intestinal peristalsis its use has been extolled in atony of the intestine, tympanites, post-operative intestinal paralysis, and chronic constipation. In all these conditions it is administered subcutaneously ($\frac{1}{80}$ gr.).

On the assumption that acetyl-choline is the chemical transmitter of the impulse at the motor endings to the skeletal muscles, it has been suggested that in diseases characterised by paresis of the skeletal muscles there might be insufficient formation or rapid destruction of acetyl-choline formed in response to a nervous impulse. Physostigmine has therefore been used in the treatment of **myasthenia gravis** on the idea that it will prevent the destruction of acetyl-choline and intensify the action of the transmitter. For this purpose it has been used in doses of $\frac{1}{80}$ to $\frac{1}{50}$ gr. by the mouth in an empty stomach or hypodermically, but the results have not been very encouraging because of its general stimulating effect on the parasympathetic system, namely, lowering of the pulse rate, increased peristalsis, nausea, and fibrillary twitchings. It has therefore been replaced by prostigmine, or used with atropine $\frac{1}{100}$ gr.

PROSTIGMIN—Dimethylcarbonate of hydroxy-phenyltrimethylammonium-methyl-sulphate. A synthetic preparation allied to physostigmine, but has a more powerful action on the intestine and little on the eye and none on the circulation. Administered subcutaneously, intramuscularly and intravenously in post-operative intestinal paresis, constipation due to atony of the intestine and retention of the urine. Also used in **myasthenia gravis**.

Dose.—0.5 mg. in 1 mil ampoules.

GLYCINE *Syn*—*Glycocol*; *Amino-acetic Acid*.—In white crystals of sweet taste. Soluble in $4\frac{1}{2}$ of water. It is used in the treatment of **muscular dystrophies**, e.g. **myasthenia gravis** on the idea that muscular weakness is due to failure of the muscles to convert creatine into creatinine for which the presence of amino-acid is necessary. Administration of glycine aids the conversion of creatine into creatinine and accelerates creatine metabolism. It is used alone or supplemented by ephedrine.

Dose.—150 grs. to 1 oz. or 10 to 30 gm. per day in two or three doses.

C OLINE

(Not Official)

A syrupy liquid occurs in organ extracts, many vegetables, ergot, and as a decomposition product of lecithin. It has been isolated from washed portions of intestines of rabbit, dog and cat.

Acetyl-choline—The acetyl derivative of choline. Prescribed in the form of **Acetyl-choline Hydrochloride**. A white hygroscopic powder. *Dose*.— $\frac{3}{4}$ gr. (0.05 gm.) subcutaneously or intramuscularly. Dangerous intravenously and ineffective when given orally.

ACTION AND USES

Acetyl-choline is about 100,000 times more powerful than choline and has four important actions, *viz.* (1) it *dilates the vessels* and causes a fall of blood pressure, this effect is direct; (2) *stimulates the post-ganglionic fibres of the parasympathetic* like muscarine, *i.e.* causes increased secretion of the salivary, lachrymal, intestinal and also the sweat glands which are innervated by the sympathetic but contains cholinergic fibres; (3) *first stimulates and then paralyzes the autonomic ganglia* (nicotine effect). Therefore the effect will vary with the dose; and (4) *stimulates the ends of all motor nerves to skeletal muscles*.

The action of acetyl-choline is short lived as it is destroyed by a specific enzyme—*choline esterase*. On the other hand eserine inhibits this action of esterase. A preliminary use of physostigmine therefore enhances the action of acetyl-choline. It increases the movements of the œsophagus, stomach, intestine and bladder. The uterus is stimulated by its direct action on the muscle though the organ is supplied by the sympathetic.

In large doses the fall of pressure is great due largely to vagus effect on the heart (slowing of rate and weakening of contraction). After atropine, small doses do not depress the heart or lower the pressure. Very large doses however (5 mg.) produce a marked rise of pressure, specially after previous destruction of the bulb and spinal cord. This is due to its effect on the sympathetic ganglia so that after a large dose of nicotine, which paralyzes the autonomic ganglia, this pressor effect is abolished.

It is present in many tissues, and it is believed that its presence, which is of the nature of hormone, maintains the normal activity of the intestine. It increases salivary and gastric secretion by stimulating the secretory endings of the vagus in the glands.

Acetyl-choline is used to lower blood-pressure in an emergency, but it will keep the pressure down only for a short time. It is also recommended in Raynaud's disease and checks the night sweats of phthisis. It should always be used *intramuscularly*, intravenous injection is dangerous, and given by the mouth it is useless.

It has been used intramuscularly to counteract paralysis of the intestine such as occurs after laparotomy and intestinal operations. It may also be used to relieve severe post-operative gas distention and pain and also post-operative *retention of urine* and in other conditions, particularly organic nervous disorders which render complete emptying of the bladder ineffective.

Since it stimulates the motor nerve endings to skeletal muscles, it has been used in the treatment of *myasthenia gravis*. (see physostigmine).

Leubret and Pery* have shown that in all cases of tuberculosis there is marked decrease of blood cholesterol, and sometimes also in the blood sugar, showing a deep humoral trouble. They recommended injection of *Choline Hydrochloride*, 2 cgm. ($\frac{1}{2}$ gr.) in 1 c.c. in all

* *British Medical Journal, Epitome*, May 10, 1930.

stages of tuberculosis and reported favourable result. The treatment is followed by a lowering of temperature, a return of the appetite with a re-establishment of the digestive functions and a gain in weight. The blood cholesterol is increased and the blood-sugar-cholesterol ratio returns to normal. When combined with calcium it gives better result in tuberculosis. The usual formula is calcium gluconate 10 p.c. and choline hydrochloride $\frac{3}{8}$ gr. in 10 c.c. of physiological solution. This is sold under the name of Injectable Calcinol. The injections are given once or twice a week.

2. Drugs Depressing the Parasympathetic endings

ELLA ONNAE FOLIUM

Belladonna Leaf. (Bellad. Fol.)

Syn.—Deadly Nightshade Leaves

Source.—The leaves and tops of *Atropa Belladonna*, collected when the plant is in flower, and dried. Contains not less than 0.3 p.c. of the alkaloids of the leaf, calculated as hyoscyamine.

Characters.—Leaves alternate below, in unequal pairs above; 5 to 25 cm. long, broadly ovate, acute, entire, glabrous, short stalked. Corolla gamopetalous, campanulate, purple.

Composition.—(1) *Atropine* (2) *Hyoscyamine*. (3) *Belladonnine*, minute quantities.

OFFICIAL PREPARATIONS

1. *Belladonna Pulverata*. **Syn.**—*Pulvis Belladonnæ*.—Leaf reduced to fine powder and adjusted, if necessary, by admixture of powdered exhausted belladonna leaf to contain 0.3 p.c. of alkaloid hyoscyamine. $\frac{1}{15}$ gr. of alkaloid in 3 grs. B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm.

2. *Extractum Belladonnæ Siccum*.—Alkaloid 1 p.c. or $\frac{1}{15}$ gr. in 1 gr. B.P. Dose.— $\frac{1}{2}$ to 1 gr. or 0.015 to 0.06 grm.

3. *Tinctura Belladonnæ*.—Contains 0.03 p.c. w/v of the alkaloid, or $\frac{1}{100}$ gr. in 30 ms. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mls.

ELLA NNAE A IX

Belladonna Root. (Bellad. Rad.)

Source.—The dried root of *Atropa Belladonna*. Contains not less than 0.4 p.c. alkaloid hyoscyamine.

Characters.—In cylindrical pieces, entire or longitudinally split up to 4 cm. in diameter at the crown; pale greyish-brown and wrinkled longitudinally. Fracture short. Internally white, starchy, with no radiate appearance.

Composition.—The same as that of the leaves (*see above*).

B.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

OFFICIAL PREPARATIONS

1. *Emplastrum Belladonnæ*.—Alkaloids 0.25 p.c.

2. *Extractum Belladonnæ Liquidum*.—0.75 p.c. of the alkaloids of the root, or $\frac{1}{15}$ gr. in 1 m. B.P. Dose.— $\frac{1}{2}$ to 1 m. or 0.015 to 0.06 mil.

3. *Linimentum Belladonnæ*.—Alkaloids 0.375 p.c.

4. *Suppositorium Belladonnæ*.—Alkaloids $\frac{1}{80}$ gr. (0.001 grm.) in each; or $2\frac{1}{2}$ ms. of the liquid extract.

NON-OFFICIAL PREPARATIONS

1. *Collodium Belladonnæ*, B.P.C. **Syn.**—*Empl. Belladonnæ Fluidum*.—Liquid extract 50, Canada balsam 4, castor oil 2, camphor 15, pyroxylin 25, alcohol (90 p.c.) 10, ether to 100.

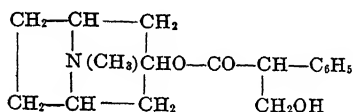
2 **Extractum Belladonnæ Viride, B P C**—A soft extract made from the leaves, containing 0.95 to 1.05 p.c. of the alkaloids of belladonna. *Dose*.— $\frac{1}{4}$ to 1 gr. or 0.016 to 0.066 grm.

ATROPINE

Atropine. (Atrop.). $C_{17}H_{23}NO_3$

Source.—An alkaloid, *dl*-hyoscyamine, obtained from *Atropa Belladonna*, *Hyoscyamus muticus*, and other plants of the family Solanaceæ.

Characters—In colourless crystals, odourless. *Solubility*—1 in 500 of water, freely in alcohol (90 p.c.), chloroform and in 16 parts of ether. The solution is *alkaline*.



Incompatibles.—Caustic alkalies and mercurial salt.

B.P. Dose— $\frac{1}{2}$ to $\frac{1}{8}$ gr. or 0.00025 to 0.001 grm.

ATROPINÆ SULPHAS

(Atrop. Sulph.)

Atropine Sulphate $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$

Source.—The sulphate of the alkaloid atropine.

Characters—In colourless crystals, odourless. *Solubility*.—In less than 1 part of water, 1 in 4 of alcohol (90 p.c.). The solution is *neutral*.

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{8}$ gr. or 0.00025 to 0.001 grm.

OFFICIAL PREPARATIONS

1. **Lamella Atropinæ**.—Each contains $\frac{1}{80}$ gr. (0.013 mg.).
2. **Oculentum Atropinæ**—0.25 p.c.
3. **Oculentum Atropinæ cum Hydrargyri Oxido**—Atropine sulphate 0.125 p.c., yellow mercuric oxide 1 p.c.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

1 **Atropinæ Methylnitrates** *Syn*.—*Eunydine*—In white soluble crystals, obtained by the action of silver nitrate and atropine methyl bromide. Valuable *antispasmodic* and less poisonous than atropine. Used with success in *congenital pyloric stenosis*. A powerful mydriatic in 1 to 2 p.c. solution. *Dose*— $\frac{1}{50}$ to $\frac{1}{30}$ gr. or 0.001 to 0.002 grm.

2 **Oculentum Atropinæ et Cocainæ, B.P.C**—Atropine sulphate 0.25 p.c. and cocaine hydrochloride about 0.5 p.c.

3. **Euphthalmim**—A synthetic compound. A 5 to 10 p.c. solution dilates the pupil like homatropine, but its effects are not so lasting.

HOMATROPINE HYDROBROMIDE

(Homatrop. Hydrobrom.)

Homatropine Hydrobromide. $C_{16}H_{21}NO_3 \cdot HBr$

Source.—The hydrobromide of an alkaloid, homatropine, prepared from tropine and mandelic acid.

Characters—A colourless crystalline powder; odourless. *Soluble* in 6 parts of water, in 18 parts of alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{3}$ gr. or 0.001 to 0.002 grm.

OFFICIAL PREPARATION

1. *Lamella Homatropinæ*.— $\frac{1}{10}$ gr. (0.65 mg.) in each.

PHARMACOLOGY

Belladonna stimulates the brain and the vital medullary centres; depresses the sensory nerve endings; motor nerve endings in the smooth muscles; secretory nerve endings; 3rd nerve in the eye; and the vagus endings. Although it is described as acting by depressing the parasympathetic nerve endings, it acts directly on the cells or peripheral receptors by preventing these being acted upon by acetylcholine.

Externally.—The unbroken skin absorbs the alkaloids of belladonna if combined with alcohol, chloroform, glycerin or fat. Exposed mucous surfaces and raw skin absorb them more rapidly. Both belladonna and atropine powerfully paralyse the peripheral terminations of the sensory nerves, especially if there is pain, and are therefore local anæsthetics and anodynes. To a much less extent they paralyse the motor and secretory nerve-endings. The blood vessels of the part first contract and then dilate.

Internally.—Atropine readily enters the blood and circulates unaltered without affecting the blood corpuscles. It chiefly affects the parasympathetic nervous system; other organs and tissues are indirectly influenced through its action on their special or secretory nerves. Therefore we will first notice its action on the nervous system proper and afterwards on other organs of the body.

Nervous system.—Its effects on the central nervous system are those of general stimulation. But it acts more powerfully on the higher divisions of the nervous axis, so that in cases of poisoning the symptoms are referred more to the brain, and consist in increased co-ordinated movements like delirium and talkativeness, whereas with strychnine, which also stimulates the central nervous system, the symptoms arise from stimulation of the lower axis of the nervous system and consist of exaggerated reflexes and convulsions.

1. *Cerebrum*.—In medicinal doses belladonna scarcely produces any effect on the convolutions, but in large doses it stimulates the central motor area causing general nervous excitement, talkativeness, mental hallucination, disordered gait and vision. The conjunctiva and face become flushed, pulse is quickened and respiration rendered frequent. Still larger doses aggravate the symptoms causing delirium and convulsion followed by stupor and coma. The reflexes become more active but the higher psychical faculties are not affected like caffeine.

2. *Medulla and cord*.—Two chief centres are powerfully

stimulated by belladonna in large doses, *viz.* (a) the respiratory; and (b) the vaso-motor. The vagal centre is affected in small doses. It also slightly increases then diminishes the reflex excitability.

3. *Sensory nerves.*—Belladonna, whether locally applied or given by the mouth, paralyses the peripheral terminations of the sensory nerves and thereby relieves pain if present. It is therefore a **local and general anodyne**. Its action is not so powerful as that of atropine. As a general anodyne atropine is inferior to morphine.

4. *Motor nerves and voluntary muscles.*—The motor nerves are slightly paralysed towards the end, but the voluntary muscles are never affected.

5. *Stomach and intestine.*—In the stomach atropine relieves pyloric spasm without interfering with the normal movements of the stomach when due to vagus stimulation but not when the sympathetic is concerned (Sollmann). In ordinary therapeutic doses however the normal movements of the intestine are not influenced nor the effects of purgatives interfered with, i.e. it does not interfere with peristalsis, but relieves the griping pains and irregular movements of the gut by the vagal endings. In large doses, as used in animal experiments, atropine increases peristalsis from its effects on the Auerbach's plexus

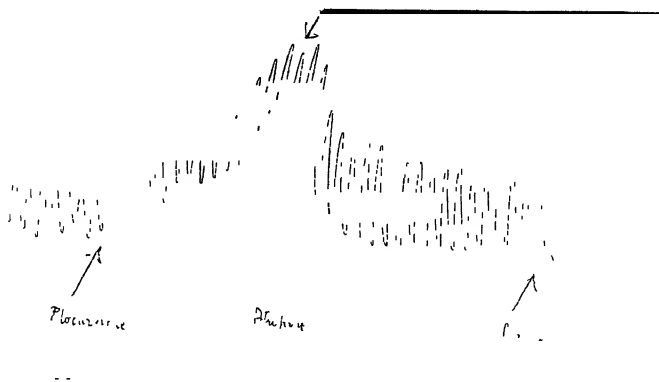


FIG. 5.—Movements of the isolated intestine.

At first arrow pilocarpine was given, note powerful contraction of the longitudinal muscle, at second arrow atropine was added when the contractions became less with normal pendulum movements, at third arrow adrenaline was applied, note complete relaxation of the muscles.

Atropine inhibits the movements of the isolated strips of intestine and will antagonise the action of pilocarpine. This effect is due to its depressing effect on the parasympathetic nerve endings. It will therefore relieve griping

when due to a drug which stimulates vagus endings, but not when due to direct stimulation of the intestinal muscles.

6. *Bladder, urethra, uterus, etc.*—The terminations of the nerves supplying the involuntary muscles of the bile duct, bladder, ureter, vesiculæ seminalis, uterus, vagina, are paralysed. Atropine therefore relieves spasm of these organs; and in cases of bile duct and ureters help passage of calculi.

7. *Third nerve in the eye.*—Atropine has the following important effects on the eye: (a) *The pupil.*—The pupil is regulated by the iris which is composed of two sets of muscular fibres—the circular which contract and the radiating which dilate. The former is supplied by the third nerve and the latter by the sympathetic fibres from the superior cervical ganglion (see fig. 3, page 224). Dilatation of the pupil may be due to either depression of the sphincter iridis or stimulation of the radiating fibres; while contraction results from the opposite influences. These stimulations or depressions may be of centre, ganglia, nerve-endings, or muscle fibres. Atropine administered internally dilates the pupils and when dropped into one eye it dilates the pupil of that eye, but has no effect on the other eye; further stimulation of the third nerve, either central or peripheral to the ciliary ganglia is without any effect on the pupil. Dilatation is due to the paralysis of the parasympathetic endings of the 3rd nerve, and since the direct stimulation of the sphincter iridis results in contraction it has no effect on the muscle. Dilatation caused by atropine is however not maximum for stimulation of the cervical sympathetic results in further dilatation of the pupil, and that after the removal of the superior cervical ganglion and subsequent degeneration of the sympathetic nerve fibres, atropine fails to dilate the pupil.

(b) *Accommodation.*—Atropine paralyses the terminations of the third nerve in the ciliary muscle and thus paralyses accommodation. It is therefore strongly cycloplegic.

(c) *Intra-ocular tension.*—As an indirect result of the dilatation of the pupil by which the flow of lymph is obstructed, atropine increases intra-ocular tension.

8. *Vagal endings in the heart.*—The vagus is the inhibitory nerve of the heart. Belladonna or atropine in small therapeutic doses ($\frac{1}{150}$ gr.) stimulates the vagus centre causing slowing of the pulse. But when large doses ($\frac{1}{75}$ gr.) are given, or small doses repeated, then quickening of the rate is observed due to depression of the vagal nerve endings. This rapidity cannot be diminished by stimulating the vagus. At times the excitement becomes so strong that the heart-sounds may be heard a few feet from the patient. With the acceleration of the pulse belladonna does not reduce

the force and tone of the heart. Since the inhibitory fibres are almost inactive at birth, atropine has no effect in increasing the heart beat in the new born child. It has also little effect in old age. The vagus effect shows both at the sinus and the auriculo-ventricular nodes, and atropine therefore checks heart-block caused by digitalis. Sollmann has shown that atropine has some action on the cardiac muscle, which can be observed in the isolated heart and on the nerve-free heart of embryonic chick but this effect on the muscle is negligible.

9. *Vagal endings in the bronchial walls.*—Both the afferent and efferent terminal filaments of the vagus are paralysed after a brief stimulation, producing relaxation of the muscular coat of the tubes, and diminishing the sensibility and reflex action (paralysis of the afferent fibres). These are the only effects produced in therapeutic doses. Thus belladonna is a **bronchial antispasmodic**. The sympathetic fibres which dilate the bronchi are unaffected by atropine. It also diminishes the bronchial secretion.

In large doses the respiration becomes quicker and deeper by the stimulation of the respiratory centre and increased formation of CO_2 , but toxic doses paralyse it and make it shallow and slow.

10. *Vaso-motor nerves and the skin.*—The action of belladonna on the blood-pressure depends on its effect on the heart. After a temporary fall the pressure rises above normal partly from its effect on the heart and partly from stimulation of the vaso-motor centre. The rise of blood-pressure is greater if it has been lowered by excessive vagus stimulation of the heart and dilatation of the blood vessels. In toxic doses the vaso-motor centre is paralysed and the blood-pressure falls. The arteries of the skin, especially those of the head and neck, are dilated in toxic doses giving rise to flushing of the face, or scarlatiniform or erythematous rash on the skin so often seen in belladonna poisoning. Some patients are specially susceptible to belladonna and a single therapeutic dose causes flushing of the skin and dryness of the mouth. This is due to idiosyncrasy.

11. *Secretory nerves.*—Atropine is a powerful paralysing agent of almost all the secretory nerve-endings in the body, thereby exercising a most powerful depressant influence on the secretions of most of the secretory organs. Its actions on these organs are given below:—

(a) *Salivary and mucous glands*—Even in small doses atropine powerfully paralyses the terminations of the secretory fibres of the chorda tympani, but not the vaso-dilator ones, so that stimulation of the chorda tympani, does not increase the flow of saliva from the submaxillary gland though its vascularity is increased. Stimulation of the sympathetic still induces secretion, this shows that although

the secretory nerves are paralysed secreting cells are not influenced in any way. It also depresses the terminations of the secretory nerves of the salivary and mucous glands. Consequently, the mouth, palate and throat become dry and red. After large doses the dryness increases so much that deglutition becomes impossible. Hence atropine is a powerful antisialagogue.

(b) *Gastro-intestinal glands*.—No effect on gastric secretion is observed when atropine or belladonna is given orally in small doses, but large doses, specially when administered hypodermically paralyse the terminations of the secretory fibres of the vagus in the stomach, and reduce or even arrest the gastric secretion. The hydrochloric acid is more reduced than pepsin or the fluid as a whole.

(c) *Liver and pancreas*.—Secretion of the pancreas depends upon the presence in the blood of secretin rather than on nerve impulse, and since atropine reduces the secretion of hydrochloric acid in the stomach which in the duodenum acts as stimulant to the formation of secretin, there is some diminution in the secretion of the pancreatic juice. The secretion of bile is little affected by atropine.

(d) *Bronchial glands*.—The secretion of the bronchial and tracheal mucus is very much diminished.

(e) *Sweat-glands*.—Given by the mouth atropine powerfully checks sweating. This it does by paralysing the terminations of the nerves in the sweat glands. The skin therefore becomes dry and hot. Applied locally it has no influence over the secretion of the sweat.

(f) *Mammary glands*.—The secretion of milk is not arrested since the secretion is largely independent of the central nervous system.

(g) *Lachrymal glands*.—Prolonged use of atropine arrests their secretion.

(h) *Kidneys*.—Here its action is uncertain. Since the kidneys are not controlled by any secretory nerves, atropine has very little effect on the amount of urine. Large doses cause retention of urine as the result of paralysis of the bladder.

Temperature.—Belladonna in moderate doses raises the temperature of the body by 3 to 4 degrees due possibly to suppression of perspiration. As the circulation fails the temperature falls.

Elimination.—It is partly oxidised in the body possibly in the liver, the unoxidised portion is excreted by the urine within 10 to 20 hours. Part of it may be broken up into tropine. Traces have been found in the milk. It increases urea, phosphates, sulphates, but not chlorides in the urine.

Toleration.—Children can bear large doses of belladonna. Old people bear it badly but some tolerance may be produced by the gradual increase of the dose. *Idiosyncrasy* to the

drug is common, some patients showing flushing, dryness of the mouth and throat and an erythematous rash even with ordinary therapeutic doses. This is often noticed amongst members of the same family, all the members being susceptible to it.

Summary of action.—1. Atropine stimulates the following centres:—(a) cerebral, producing delirium; (b) vital medullary centres—respiratory, vagal and vaso-motor. 2. It depresses (a) the sensory nerve-endings; (b) the motor nerve-endings in the smooth muscles of the viscera, thus allays abnormal contractions of the muscles of the bronchi, stomach, intestine, bile duct, etc.; (c) the parasympathetic endings of the third nerve of the eye; and (d) the vagus nerve-endings—making the heart free from the inhibitory nerve control.

Methyl and ethyl atropines do not cause tetanus in frogs and paralyse the motor ends, but they act like atropine on the eye, heart, etc.

Acute toxic action.—The symptoms that follow a moderate dose of atropine are (1) dry mouth and throat, (2) dilated pupil, (3) dim vision, (4) dry skin, (5) dysuria, (6) dysphagia, (7) delirium (wild). Erythematous rashes are common. At the *post-mortem* all organs are in a state of venous congestion due to asphyxia.

The symptoms of poisoning have been observed after the application of plaster, glycerin of belladonna, or liniment.

Treatment.—Emetics or pump. Tannin, tea, charcoal; morphine $\frac{1}{2}$ gr. in the early stage, caffeine, or pilocarpine $\frac{1}{2}$ gr. hypodermically, repeated till the mouth becomes moist. Physostigmine or chloral hydrate are also recommended. Stimulants, hot bottles, artificial respiration. Ice to the head for delirium. As the poison is eliminated by the urine, the bladder should be emptied now and then to prevent reabsorption.

THERAPEUTICS

Externally. Skin.—As a local *anodyne*, the liniment, plaster or ointment are largely employed to soothe irritability or pain in neuralgia, soreness of muscles, etc. Chloroformum belladonnæ (1 of liquid extract in 2), or ung. atropinæ is most powerful in this respect. Occasionally atropine injected subcutaneously as near the nerve as possible does more good in neuralgia, especially in sciatica, than any local application. Glycerinum belladonnæ or collodium belladonnæ may be applied over threatening boils, abscesses, etc. In the form of an ointment either alone or better still with conium, belladonna lessens the spasm of anal fissure and the pain and irritation of piles.

Female diseases.—The plaster or the extract with glycerin is used to stop the secretion of milk. But the same results are obtained by the application of simple adhesive plaster, or yellow wax and olive oil. Extract of belladonna with glycerin (5 to 10 grs. to 1 oz.) in cotton wool may be used as a tampon in inflammation of the womb or cervix.

A pessary containing the extract 2 grs., tannic acid 7 grs., and cocoa-butter, *q s.* is very serviceable in leucorrhœa with ulcerated os. A suppository containing extract 1 gr. is an excellent application to relieve the pain of spasmodic and neuralgic dysmenorrhœa.

Eye.—A solution of atropine is dropped into the eye to dilate the pupil to facilitate examination of the internal eye posterior to the pupil, and paralyse the accommodation in fitting glasses. Smaller doses (0.1 to 0.01 p.c. solution) will dilate the pupil but stronger solution (1 p.c.) is required to paralyse accommodation. As a rule accommodation does not recover till after 5 to 7 days, and the pupil does not become normal till after one to two weeks. Where only temporary mydriasis is required, as in estimating errors of refraction, homatropine may be used in preference to atropine as the effects pass off more quickly and there is less likelihood of toxic effects from absorption. In inflammatory conditions it is applied to give rest to the iris and ciliary muscle, and in iritis to prevent formation of adhesions to the lens and cornea. It is contra-indicated where there is suspicion of glaucoma as by increasing intra-ocular pressure it may either aggravate the disease already present or may precipitate an acute attack.

Internally.—Atropine is indicated in all conditions where a depression of the parasympathetic nerve-endings is required. It is therefore used to diminish secretion of sweat, saliva, or tears; to reduce spasm of involuntary muscles, *e.g.* of bronchi, stomach, intestine, sphincter of the gall-bladder, urinary bladder and uterus; and to stimulate the respiratory centre.

Alimentary canal.—Atropine sometimes checks mercurial salivation. In small doses, frequently repeated, alone or in combination with aconite, belladonna (*Tinct.*) checks acute tonsillitis. As it lessens the secretion of gastric juice and the motor activity of the stomach, atropine may be used in hyperchlorhydria, gastric ulcer, etc., and is specially valuable in acute conditions with severe pain. The extract is often combined with purgatives either to increase their activity or lessen griping. It has been used with some success in some forms of constipation, and may be given in habitual or chronic constipation and painful defæcation. In obstinate constipation Trousseau recommends the extract $\frac{1}{8}$ to $\frac{1}{4}$ gr., night and morning.

In full doses ($\frac{1}{60}$ gr.) atropine is useful in sea sickness where it acts by paralysing the vagus. In fact persistent vomiting often results from pyloric spasm which is checked by atropine.

Belladonna is often effective in intestinal obstruction due to fæcal stasis, atony of the intestine and reflex stricture; but to be of any use it should be given in large doses

(20 to 30 ms.) frequently till the symptoms of poisoning appear. Alone or with opium it is useful in peritonitis, enteritis and appendicitis. It also relieves the pain of biliary, intestinal and lead colic by paralysing the sensory nerve-terminations and relaxing the involuntary muscular fibres, and since it does not cause constipation it is preferable to morphine specially in lead colic. A hypodermic injection of atropine ($\frac{1}{20}$ gr.) often helps reduction of hernia or volvulus.

Heart and circulation.—Belladonna relieves palpitation, pain and distress of the heart. For this purpose a plaster is often applied over the cardiac region. As a preliminary to general anæsthesia atropine is injected subcutaneously to stimulate the respiratory centre, to prevent salivation, bronchial secretion, and in chloroform anæsthesia to check excessive vagus stimulation. It is used in **bradycardia** or **partial heart-block**, but has no effect in complete and permanent heart-block. On the other hand when the slowness of the heart is due to disease of the muscle itself atropine is of no use. In fact its use has been suggested as a means of diagnosis between myogenic and neurogenic bradycardia. In these cases atropine must be pushed to the limit of physiological tolerance. As it has very little effect in accelerating the pulse in typhoid fever where the heart muscle is affected by the toxin, it has been used to differentiate typhoid from other fevers. The method is to ascertain the normal pulse rate which is taken every minute until it is steady, when $\frac{1}{8}$ gr. of atropine is given hypodermically. After 25 minutes, the pulse rate is again taken and recorded minute by minute until the temporary acceleration is over (which takes about 15 to 20 minutes). If the acceleration is within 10 per minute, the infection is probable. This test is observed in the 2nd week and in patients not over 80 years.

Respiratory tract.—Belladonna is extremely useful in many spasmodic affections of the air-passages, such as asthma, spasmodic bronchitis and whooping cough. A subcutaneous injection of atropine often gives great relief in spasmodic asthma. In whooping cough* it must be given freely before we may expect any decided improvement. In nasal catarrh with profuse discharge atropine gives immediate relief. As it stimulates respiration it may be used in pneumonia, in narcotic poisoning, and as a preliminary to ether anæsthesia; and is often combined with morphine to

*R

Pot brom	grs 2-4
Pot bicarb.	grs. 2
Sp. ammon, aromat.	ms. 4
Tinct. bellad	ms. 2-5
Syr prun. serot.	ms 15
Aqua anethi	ad oz. $\frac{1}{2}$

In whooping cough for a child 2-4 years.

counteract the depressing effect on respiration of the latter. It has also been used to prevent anaphylaxis.

Skin.—Atropine (1 to 2 ms. of the solution, or $\frac{1}{160}$ gr. hypodermically) arrests excessive sweating. It is therefore an excellent remedy for night-sweats of phthisis.

Nervous system.—Belladonna is now rarely used in nervous diseases. It sometimes controls delirium in fevers. Atropine is used in the treatment of post-encephalitic parkinsonism where it gives great relief by diminishing muscular rigidity, reducing tremors, and lessening excessive lachrymation and salivation. The method consists in ascertaining the *maximum dose* that causes improvement by a daily graduated increase of dose. When such increase yields no further benefit, the dose is similarly decreased until the return of the symptoms show that the dose is too small. Begin with a total daily dose of 0.5 mgrm ($\frac{1}{20}$ gr.) in two doses and increase by 0.5 mgrm. daily, spread over three doses, till no further improvement is noticed; keep on at this maximum dose for a few days, then reduce the dose by 0.25 mgrm. daily until a point is reached at which subjective and objective symptoms return. A slightly higher dose than this is the *optimum dose*. In mild cases the optimum dose is 3 to 8 mgrm. ($\frac{1}{20}$ to $\frac{1}{8}$ gr) daily; in severe cases it varies from 12 to 24 mgrm.

Genito-urinary tract.—It is a very useful remedy in incontinence of urine in children, and retention from over-activity of the sphincter of the bladder. Here it acts by relaxing the spasmodic contraction of the sphincter. It may stop nocturnal emissions in persons whose genitals are weak and relaxed, and when discharge takes place without dream or orgasm. But extract of hyoscyamus and camphor are better for this purpose. It is very useful in allaying the pain and helping the expulsion of renal calculus, but in order to obtain these effects it must be given in large doses until toxic action is produced (W. Murray). Cystitis, dysuria, urethral spasms and, in fact, any kind of pain in the pelvic organs, *e.g.* dysmenorrhœa, can be removed by belladonna either administered in the form of a suppository or by the mouth.

Antidotes to poisons.—Atropine may be successfully used as a physiological antidote in poisoning by morphine, pilocarpine, physostigmine, chloroform, aconite, poisonous mushrooms (muscarine), nitroglycerin, gelsemine and hydrocyanic acid.

Prescribing hints.—A porous belladonna plaster is the best to use as it causes less itching and irritation. Collodion belladonna may be painted over an uneven surface in its stead. Atropine may be given in tablets, pills or in solution. Hypodermically it is often combined with morphine to counteract its unpleasant physiological effects and to

increase its sedative virtue. 10 ms. of the tincture every 4 hours to young children for *whooping cough*; and 30 to 40 ms. of the same every 1 or 2 hours during an *attack of renal colic* until atropism—dryness of the throat, dilatation of the pupils and delirium—sets in are not unsafe to use in these cases. Caustic fixed alkalies destroy the alkaloids of belladonna, but carbonates and bicarbonates of sodium and potassium do not do so.

Homatropine hydrobromide may be applied into the eye either in solution (4 grs. in 1 oz. of water), or as a disc, or dissolved in castor oil with cocaine. The object of mixing it with castor oil is to prevent it from being washed away by the tears. As it dilates the pupil more quickly (within an hour) and the effects are of shorter duration (passing off within 24 hours), it is used in preference to atropine, moreover it has less tendency to increase intra-ocular tension. It is therefore a more convenient drug for examination of the eye, unless it is desired to paralyse completely the ciliary muscles.

Y SCYA US

Hyoscyamus. (Hyoscy.)

Syn.—Henbane Leaves; Hyoscyami Folia.

Source.—The dried leaves and flowering tops of *Hyoscyamus niger*. Contains not less than 0.05 p.c. of the alkaloid hyoscyamine.

Characters.—Leaves vary in length up to 25 cm., mostly sessile; exstipulate, triangular-ovate or ovate-oblong, acute, sinuate, pale green. Furnished with glandular hairs particularly underneath. Branches cylindrical and glandular hairy, corolla yellow; odour strong; taste, bitter and slightly acid when fresh.

Composition.—Chief alkaloids are (1) *Hyoscyamine*. (2) *Atropine*. (3) *Hyoscine* (Scopolamine). (4) A poisonous oil.

Incompatibles.—Liquor potassæ, lead acetate, silver nitrate, and vegetable acids.

B.P. Dose.—3 to 6 grs. or 0.2 to 0.4 grm.

OFFICIAL PREPARATIONS

1. *Extractum Hyoscyami Liquidum*.—Contains 0.05 p.c. w/v of the alkaloid hyoscyamine, or $\frac{1}{20}$ gr. in 6 ms. B.P. Dose.—3 to 6 ms. or 0.2 to 0.4 mil.

2. *Extractum Hyoscyami Siccum* Syn.—*Extractum Hyoscyami*.—0.3 p.c. of the alkaloid hyoscyamine, or $\frac{1}{30}$ gr. in 1 gr. B.P. Dose— $\frac{1}{4}$ to 1 gr or 0.016 to 0.06 grm

3. *Tinctura Hyoscyami*.—Contains 0.005 p.c. w/v of the alkaloid hyoscyamine, or $\frac{1}{200}$ gr. in 60 ms. B.P. Dose—30 to 60 ms. or 2 to 4 mils.

4. *Pilula Colocynthis et Hyoscyami*.—12.5 p.c. of extract hyoscyamus. B.P. Dose.—4 to 8 grs or 0.25 to 0.5 grm.

PHARMACOLOGY

Hyoscyamine, the principal alkaloid in hyoscyamus, is isomeric with atropine and is easily converted into the latter in the presence of a fixed alkali at the ordinary temperature.

Most of the properties of hyoscyamus must therefore be identical with those of belladonna and stramonium. The following are however the chief points of difference:—(1) Hyoscyamus because of the presence of hyoscyne excites the brain less and has a marked and rapid *sedative and soporific effect on the cerebrum*. (2) It has also more pronounced *sedative action on the spinal cord*. (3) It is also sedative to the intestine and is more efficacious in relieving griping and irregular contraction. (4) It is *not a powerful stimulator of the heart*. (5) It relieves *irritation of the urinary passages*, especially that of the bladder. This it does by depressing the ends of the nerves of the mucous membrane, and controlling the spasms of the muscular fibres. (6) *Intra-ocular tension* is less affected.

THERAPEUTICS

Besides its use in those cases where belladonna is indicated, it is employed (1) to soothe cerebral excitement and produce sleep, as in mania and insomnia; (2) to lessen cardiac asthma; (3) to correct the painful griping of purgatives; (4) to relieve vesical spasm in cystitis, prostatitis, calculus, etc., often in combination with other urinary sedatives as buchu, and the alkalies; and (5) to relieve cough, as in bronchitis.

Children can bear very large doses, while the old and the weak cannot.

Y SCINAE Y I U

(Hyoscin. Hydrobrom)

Hyoscyne Hydrobromide. $C_{17}H_{21}O_4N \cdot HBr, 3H_2O$

Syn.—Scopolamine Hydrobromide.

Source.—The hydrobromide of an alkaloid, *l*-hyoscyne (*l*-scopolamine); obtained from various solanaceous plants.

Characters.—In colourless, transparent, rhombic crystals. Soluble 1 in 4 of water.

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{16}$ gr. or 0.0003 to 0.0006 gm.

OFFICIAL PREPARATION

1. Oculentum Hyoscinæ.—Contains 0.125 p.c. hyoscyne hydrobromide.

PHARMACOLOGY AND THERAPEUTICS

Hyoscyne paralyses the parasympathetic nerve-endings like atropine, but its effects are more rapid and powerful, though of brief duration. Like atropine it *paralyses the vagal endings* in the heart, but this effect is not elicited in therapeutic doses and the pulse rate is not altered. It allays pain, dilates the pupil, and checks secretion. A solution of 1 in 500 will act as a mydriatic and paralyse

accommodation but unlike atropine the effect is more rapid and passes off within 3 to 5 days. The oculentum, or a 0.2 p.c. solution is used as a mydriatic in preference to atropine.

On the central nervous system it acts as a narcotic and has a sedative action on the convulsions producing sleep which lasts for 5 to 8 hours, and since the patient remains quiet for several hours afterwards it is largely employed as a narcotic in mania, insanity, delirium tremens, tetanus, etc. It has the advantage over morphine in that it acts by quieting reflex and in not producing a habit. It has however certain unpleasant side effects and produces mydriasis, cycloplegia and dryness of the mouth. It is also used in chorea and paralysis agitans in which conditions it reduces the movements and tremors; and relieves the rigidity and muscular hypertonus in post encephalitic parkinsonism ($\frac{1}{150}$ gr. a day increased to $\frac{1}{50}$ gr. or more). Here it also reduces salivation and ocular crises. Because it reduces salivation and produces dryness of the mouth it should be given after meals. Its disadvantage is toxicity, the margin of safety between the therapeutic and lethal dose being small.

Large doses do not necessarily produce more profound sleep, but give rise to delirium and excitement like atropine. Its use is not without danger for it depresses the respiratory and vaso-motor centres, and several cases of collapse following its use are on record. The commercial specimens vary much in purity.

A combination of scopolamine and morphine is sometimes used for the production of general anæsthesia. Scopolamine hydrobromide $\frac{1}{200}$ gr. and $\frac{1}{2}$ gr. of a morphine salt is injected on the night previous to the operation, and a similar or larger dose in the morning before the operation. This usually produces deep sleep and the patients do not wake till some hours after the operation, thus escaping the most painful period. Smaller doses may be given to produce basal narcosis prior to the use of volatile anæsthetics (see page 166). Scopolamine-morphine anæsthesia, "twilight sleep," is now advocated during the second stage of labour in place of chloroform (hyoscine hydrobromide $\frac{1}{150}$ gr. with morphine sulphate $\frac{1}{8}$ to $\frac{1}{4}$ gr.). Occasionally however it causes cessation of uterine contractions and has a tendency to prolong labour, and the child may be born apnœic. Twilight sleep sometimes makes the patient maniacal, at least temporarily.

BULBOCAPNINE. (*Not official*). $C_{15}H_{19}O_4N$.—One of the alkaloids obtained from the tubers of *Dicentra canadensis* and *Corydalis tuberosa*. Insoluble in water but soluble in alcohol. It produces in cats and dogs a peculiar narcotic and cataleptic condition. The animal appears stupid and lethargic, the muscles become stiff and remain in the same position in which they are placed. This effect is counteracted by cocaine, specially in monkeys but is less effective in cats.

It is a powerful depressant to the cerebral psychomotor and motor

cortex and has been introduced for the relief of various forms of tremors associated with *chorea*, *multiple sclerosis*, *paralysis agitans* and *encephalitis*.

Dose.— $1\frac{1}{2}$ grs. or 0.1 gm. by mouth in the form of tablets or subcutaneously.

HARMINE. (*Not official*). *Syn.*—*Banisterine*—An alkaloid obtained from *Peganum Harmala*. *Harmalol hydrochloride* is generally used in doses of $\frac{1}{2}$ to $\frac{3}{4}$ gr or 0.02 to 0.04 gm.

It is largely used in the treatment of post-encephalitic parkinsonism either alone or in combination with hyoscyne. It diminishes rigidity and tremors together with salivation and improves voluntary movements. Its effects are transient although its prolonged administration is not followed by any unpleasant by-effects. It may be administered by the mouth or as an injection.

ST AMONIUM

Stramonium. (Stramon.)

Source—Dried leaves and flowering tops of *Datura Stramonium*, and of *D. tatula*. Contains not less than 0.25 p.c. of the alkaloids of stramonium, calculated as *hyoscyamine*, or $\frac{1}{16}$ gr. in 3 grs.

Characters—Greyish-green, ovate, petiolate, 8 to 25 cm. long, unequal at the base, with dentate margin and acuminate apex. Taste, saline and bitter. The leaves are minutely wrinkled.

Composition.—Contains *hyoscyamine*, *atropine* and *hyoscyne*. *Daturine* is probably a mixture of atropine and hyoscyamine.

B.P. Dose.— $\frac{1}{4}$ to 3 grs. or 0.03 to 0.2 gm.

OFFICIAL PREPARATIONS

1. **Tinctura Stramonii.**—Contains 0.025 p.c. w/v of *hyoscyamine*, or $\frac{1}{16}$ gr. in 30 ms. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils

2. **Extractum Stramonii Siccum.**—Contains about $\frac{1}{16}$ gr. in 8 grs. or 1 p.c. of the alkaloids of stramonium calculated as *hyoscyamine*. B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 gm. In post-encephalitic and similar conditions:—1 to 8 grs. or 0.06 to 0.5 gm.

3. **Extractum Stramonii Liquidum.**—Contains 0.25 p.c. of the alkaloids of stramonium, or $\frac{1}{16}$ gr. in 3 ms. B.P. Dose.— $\frac{1}{4}$ to 3 ms. or 0.03 to 0.2 mil.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Its action resembles that of belladonna, but it has a much more powerful effect in relaxing the muscular coat of the bronchial tubes, and it may cause irregularity of the heart's action. It is used for the relief of the paroxysms of *asthma*, for which purpose it may be smoked as cigarettes, or the fumes may be inhaled, or it may be given internally. When combined with potassium nitrate, lobelia, black tea and oil of anise it resembles the well-known *Himrod's*, *Bliss's* and *Green Mountain Cure* (see page 80). *Cannabis Indica* is also an excellent adjuvant.

Like atropine and hyoscyne, stramonium also relaxes the increased muscle tone of the parkinsonian. It may be prescribed either in the form of the tincture in doses of 10 ms. up to a drachm or more three times daily, or the dry extract may be used in the form of a pill.

Toxicology.—Poisoning by stramonium is fairly common in England, and the seeds of *Datura alba* and *D. fastuosa* are largely

used by the *road poisoners in India*, who mix them with food, or give them to their victim to smoke, with the object of robbery.

The *symptoms* are dryness of the throat, giddiness, flushing of the face, dilatation of the pupils, and a peculiar form of delirium associated with ludicrous movements followed by coma which may end in death.

Treatment—Emetics, stomach-pump, stimulants, cold affusion, artificial respiration. If much delirium, give opium, but opium is less useful in these cases than atropine in opium poisoning.

Brunton recommends the cautious use of physostigmine, and Ringer advises pilocarpine nitrate in $\frac{1}{4}$ to $\frac{1}{2}$ grain doses.

CLASS D: Drugs acting on the Ganglia and the Motor Nerve-endings

Lobelia (*see* p 318), Curara, Nicotine, Conium, Gelsemium, Sparteine

CURARA. (Not official) *Syn*—Uraia, Ouraia, Woorara, Woorai. The South American arrow-poison, prepared from the bark and sapwood of *Strychnos toxifera*

Composition—The active principle is *curarina* or *curarine*, a most powerful poison. It exists as a brown powder, or deliquescent prisms, with an intensely bitter taste, soluble in water and alcohol, the latter solution being slightly fluorescent, is not alkaline in reaction and forms no true salts.

Dose.— $\frac{1}{32}$ to $\frac{1}{8}$ gr. or 0.003 to 0.03 g.m. hypodermically

PHARMACOLOGY

Nervous system.—It paralyses the motor nerve-endings throughout the whole body whenever a sufficient quantity enters the blood stream. In large doses it paralyses the autonomic sympathetic ganglia. The sensory nerves are unaffected by curare.

Curare, as a rule, *only produces its physiological effect if given hypodermically*, and when taken into the stomach soon after food no results are observed. This is due to the fact that it is excreted by the kidneys more quickly than it is absorbed from the stomach and that when absorbed it is detoxicated in the liver and other tissues.

THERAPEUTICS

Curare is chiefly used in the physiological laboratory but is also one of the drugs suggested for the treatment of tetanus and other convulsive diseases. Unfortunately however effective doses paralyse the respiration and is too dangerous. It has been recommended as a palliative in hydrophobia.

NICOTINE. (Not official).—A colourless, hygroscopic, volatile liquid alkaloid obtained from *Tobacco*.

ACTION AND USES

Its actions are distributed over the cerebrum, medulla and cord, the sympathetic and parasympathetic ganglia, and the motor end-plates of the voluntary muscles. These are first stimulated and then depressed, whether it is applied locally, taken internally, or given by injection.

The heart is first slowed and then accelerated. The initial slowing is due to stimulation of the vagal centre and excitation of the ganglion cells on the course of the vagus. This is followed by depression when the sympathetic effect predominates causing acceleration of the heart. The blood pressure rises enormously from constriction of the vessels, due partly to stimulation of the vaso-motor centre, but also from excitation of the sympathetic ganglion cells, particularly those of the solar plexus. This effect is however soon followed by fall of pressure. Nicotine therefore causes first slowing of the heart and rise of blood pressure followed by acceleration and fall of pressure.

It stimulates the respiratory centre and the breathing becomes quicker and deeper. Depression soon follows and death takes place from respiratory failure. The bronchial muscles are relaxed after a transient contraction.

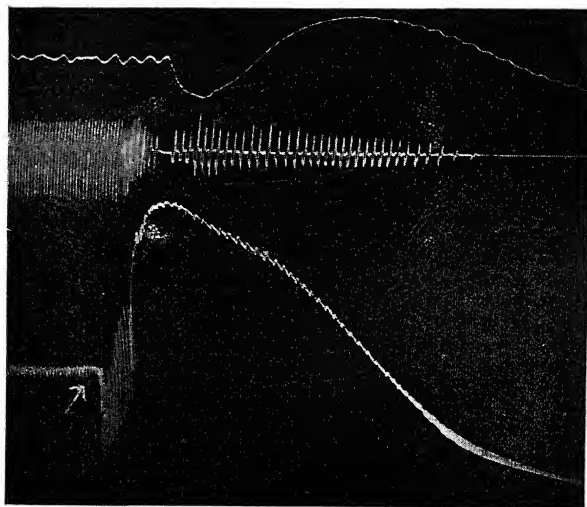


FIG. 6.—Dog. Blood-pressure, Respiration and Intestinal Volume.

At point of arrow a small injection of nicotine was given. Note slight fall of blood pressure, slowing of the heart from parasympathetic stimulation and increase of respiration from stimulation of the centre. These are followed by rise of pressure and depression of respiration. Intestinal volume is diminished during the rise of pressure from constriction of the vessels of the splanchnic area, the vessels are dilated during the fall of pressure.

It causes through central effect nausea and vomiting. The secretions of saliva, sweat and lachrymal glands are increased from stimulation of the ganglion cells on the secretory nerves; these are diminished after large doses. The smooth muscles are also affected through the ganglia on the nerves supplying them so that these are depressed after a period of stimulation. The stomach and the intestinal tract are powerfully contracted and there may be diarrhoea. These are subsequently paralysed.

Nicotine is not used in medicine, but its use has been suggested in post-encephalitic parkinsonism, specially in those cases where voluntary muscular control is intact, but movement is hampered by excessive plastic tone. Initial dose is $\frac{1}{16}$ gr. three times daily.

CONII FOLIUM. (Not official). *Syn.*—Hemlock Leaves.—The fresh leaves and young branches of *Conium maculatum*, collected when the fruit begins to form. Contains (1) *Coniine*. (2) *Methylconine*. (3) *Conhydrine*. (4) *Conic Acid*.

NON-OFFICIAL PREPARATION

1. **Unguentum Conii.** *Syn.*—Hemlock Ointment.—Extract of conium 7 p.c. in glycerin and simple ointment.

ACTION AND USES

Applied to the mucous surface it depresses the sensory and motor nerve endings, particularly the former. The ointment was formerly

DRUGS DEPRESSING SENSORY NERVE ENDINGS 251

used to relieve itching of pruritus ani and the pain and spasm of hæmorrhoids.

It paralyses the motor nerve-endings similar to curara producing ascending motor paralysis. It also paralyses the sympathetic ganglia after a brief stimulation. The inhibitory ganglia of the vagus in the heart are also paralysed after slight stimulation so that the heart is first slowed and then accelerated. Death takes place from respiratory failure while the heart still beats.

It dilates the pupil, impairs accommodation and causes ptosis from paralysis of the endings of the 3rd nerve.

GELSEMI RADIX. (Not official).—The dried rhizome and root of *Gelsemium nitidum*, the Yellow Jasmine. Contains—(1) *Gelsemine*, a crystalline alkaloid. (2) *Gelseminine*, mixture of alkaloids, and *gelsemic acid*, fats, resins, oils.

NON-OFFICIAL PREPARATION

1. *Tinctura Gelsemii*—1 in 10 Dose—5 to 15 ms or 0.3 to 1 mil.

ACTION AND USES

The symptoms of poisoning are more or less the same as observed after conium, viz. diplopia, ptosis, dilatation of the pupil, staggering gait and sleepiness, and finally arrest of respiration.

The heart is depressed in toxic doses with fall of blood-pressure from its action on the vagal ganglia. Its effects on the nervous system are the same as observed in conium poisoning except that gelsemine is more depressant. It paralyses the nerve centres first and the endings only after large doses. It causes paralysis of all the muscles of the body by depressing the cells of the anterior cornua of the cord. The motor nerve-endings are affected after large doses.

The tincture is used in neuralgia and migraine, specially neuralgia of the fifth nerve. It may be used alone or better with butyl-chloral hydrate.

SPARTEINÆ SULPHAS. (Not official) A salt of an alkaloid derived from *Scoparia cacumina*, broom tops. In colourless, odourless crystals with a saline bitter taste. Soluble, 2 in 1 of water.

Dose.—1 to 2 grs. or 0.06 to 0.12 grm.

ACTION AND USES

Sparteine resembles conine in its action but is less poisonous. It has little effect on the central nervous system. Large doses paralyse sympathetic ganglia and the motor nerve-endings. The heart is slowed and weakened from stimulation of the vagus and at one time it was used in place of digitalis, but in view of the above facts its use as a cardiac stimulant has been given up. It is however less poisonous than conium.

CLASS E: Drugs Depressing the Sensory Nerve-endings

Local anaesthesia may be produced by various means. Cold, applied either in the form of ice, or produced by spraying some volatile substance like ether or ethyl chloride, will produce anaesthesia in a localised area. Since this effect lasts only for a few seconds, cold can only be utilised for minor operations, as for instance in opening an abscess cavity or for inserting an exploratory needle, etc. Lasting anaesthesia by this method is not possible as prolonged freezing lowers the vitality of the part and produces a tendency to sloughing. Similarly CO₂ snow not only produces anaesthesia by local freezing, but also destroys superficial tissues with which it comes in contact. Partial anaesthesia is also produced by rendering the part anæmic, as by the application of Esmarch's bandage or by the use of adrenaline as often done with cocaine.

Drugs depressing the periphery of the sensory nerves may produce

local anæsthesia by lessening the tactile sensibility of a surface to which they are applied. The most important method of producing local anæsthesia is by the use of certain drugs, specially cocaine and its derivatives, phenol, urea quinine, hydrocyanic acid dilute, etc. An ideal anæsthetic should produce paralysis of the sensory nerves or nerve-endings only temporarily, and in concentration much lower than what will cause destruction of tissues.

With the introduction of many different preparations and with the advance of our knowledge, local anæsthetics are now extensively used for many operations which were formerly performed under general anæsthetics. In fact certain operations are now performed under local anæsthetics in preference to chloroform and ether. The different methods adopted for the production of local anæsthesia are as follows:—

1. Subcutaneous injection.
2. Intraspinal anæsthesia
3. Infiltration anæsthesia.
4. Regional anæsthesia.

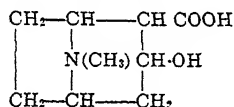
These will be discussed more fully under cocaine.

Local anodynes act only when pain is present. They relieve pain either by directly paralyzing the nerve-endings or by cental effect. They are aconite, belladonna, veratrine, phenol, chlorotone, menthol, acid hydrocyanic dilute, creosote, alcohol, ether, chloroform, opium, etc.

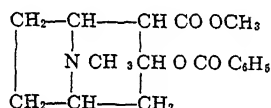
COCAINA

Cocaine (Cocain.). $C_{17}H_{21}NO_4$

Source.—It is *methylbenzoyllecgonine*. Obtained from the leaves of *Erythroxylum Coca*, and other species of *Erythroxylum*, or by synthesis from ecgonine.



Ecgonine



Cocaine

Characters.—Colourless crystals; odourless, with a bitter taste, followed by tingling and numbness. Almost *insoluble* in water, soluble in 10 parts of alcohol (90 p.c.), in 4 parts of ether, 2½ parts of olive oil and in 120 parts of liquid paraffin.

B.P. Dose.— $\frac{1}{5}$ to $\frac{1}{4}$ gr. or 0.008 to 0.016 grm.

COCAINAE Y OC LO I U

(Cocain. Hydrochlor.)

Cocaine Hydrochloride. $C_{17}H_{21}NO_4 \cdot \text{HCl}$

Source.—The hydrochloride of the alkaloid cocaine.

Characters.—In colourless, transparent crystals; odourless; taste bitter. **Solubility.**—In 0.5 part of water, 1 in 3 of alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{5}$ to $\frac{1}{4}$ gr. or 0.008 to 0.016 grm.

OFFICIAL PREPARATIONS

1. **Oculentum Cocainæ**—Cocaine hydrochloride 0.25 p.c.
2. **Lamella Cocainæ.**— $\frac{1}{5}$ gr. (1.3 mg.) in each.
3. **Trochiscus Krameriae et Cocainæ.**— $\frac{1}{50}$ gr. (0.003 grm.) of cocaine hydrochlor. in each.

A YL CAINAE Y C LO IDUM

Amylocaine Hydrochloride. (Amylocain. Hydrochlor.)

Syn—"Stovaine."

Source.—May be prepared by the action of magnesium ethyl bromide on dimethylaminoacetone

Characters.—Colourless, crystalline powder; taste, bitter, followed by a transient insensibility of the tongue. *Soluble* in 2 parts of water, and in 3 parts of dehydrated alcohol.

B.P. Dose.—By mouth and subcutaneously.— $\frac{1}{3}$ to $\frac{3}{4}$ gr. or 0.02 to 0.05 grm. By intrathecal injection.— $\frac{1}{3}$ to $1\frac{1}{2}$ grs. or 0.02 to 0.1 grm.

EN OCAINA

Benzocaine. (Benzocain.)

Syn.—"Anæsthesine"; Ethyl Aminobenzoate.

Source.—May be prepared by the reduction of ethyl *p*-nitrobenzoate.

Characters.—A white, crystalline powder; odourless; taste, slightly bitter, followed by a sensation of numbness. *Soluble* in 2500 parts of water, in 8 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

TH CAINA

Orthocaine. (Orthocain.)

Syn.—"Orthoform."

Source.—Prepared by esterifying with methyl alcohol the reduction product of 3-nitro-4-hydroxy-benzoic acid.

Characters.—A white, or faintly yellow, crystalline powder; no odour or taste. Sparingly *soluble* in water; soluble in 7 parts of alcohol (90 p.c.), in 50 parts of ether, readily in solution of caustic soda.

B.P. Dose.— $1\frac{1}{2}$ to 3 grs. or 0.1 to 0.2 grm.

P CAINA HY C L I U

Procaine Hydrochloride. (Procaïn. Hydrochlor.)

Syn.—Ethocaine Hydrochloride; "Novocaine." "Kerocaine."

Source.—By the interaction of chloroethyldiethylamine and sodium *p*-aminobenzoate.

Characters.—Colourless, crystalline powder; odourless; taste, weakly bitter, followed by a transient numbness of the tongue. Stable in air. *Soluble* in 1 part of water, and in 8 of alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.; subcutaneously up to 15 grs. or 1 grm.; intrathecally up to $2\frac{1}{2}$ grs. or 0.15 grm.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES OF COCAINE

1. *Inj. Novocainæ et Adrenalinæ*, R. O. H.—Novocaine 8 or 16 grs., adrenaline solution 24 ms., sterile water to 1 oz. *Dose*.—Up to 1 dr. of the 2 p.c.

2. *Eucaine Hydrochloride*, U. S. P. *Syn*—*Eucaine*, *Betaeucaine Hydrochloride*.—In small, white, opaque crystalline powder, soluble about 1 in 30 of water. *Dose*— $\frac{1}{8}$ to $\frac{1}{2}$ gr. or 0.008 to 0.03 grm.

3. *Tropacocaine*. *Syn*—*Benzoyl-pseudo-tropine*.—Obtained from Java cocoa. Is alleged to be safer, more rapid, and less irritating to the eye, without dilating the pupil. Its hydrochloride is freely soluble in water. Very costly. Used in 5 p.c. solution.

4. *Alypin*. *Syn*—*Amydinaine Hydrochloride*, *Benzoyl-tetramethyl-diamino-ethyl-dimethyl-carbinol hydrochloride*.—A white crystalline powder. Readily

soluble in water, giving solution of a neutral reaction. A *local anæsthetic*, used hypodermically for minor operations and in ophthalmic practice. It is equal in intensity and toxicity to cocaine. May be used in strengths of from 1 to 4 p.c. *Dose*.— $\frac{1}{100}$ to $\frac{1}{2}$ gr. or 0.003 to 0.03 gm.

5. *Butyn*.—A procaine derivative containing *butyl* in place of *ethyl* and *propanol* in place of *ethanol*. A white amorphous powder, freely soluble in water. Toxicity almost equal to cocaine but acts more powerfully and the effects last longer. *Dose*.—Hypodermically, 1 c.c. or more of $\frac{1}{2}$ or more p.c. solution.

6. *Borocaine*. *Syn*.—*Ethocaine Borate*.—A white crystalline powder. Neither toxic nor irritant. Being a salt of weak acid, in solution yields free alkaloidal base by hydrolysis. *Dose*.— $\frac{1}{2}$ to $1\frac{1}{2}$ grs. or 0.02 to 0.1 gm.

7. *Benzamine Lactate*. *Syn*.—*Eucaine Lactas*.—A white crystalline powder soluble in 5 parts of water, and in 8 parts of alcohol (90 p.c.). *Dose*.— $\frac{1}{2}$ to $\frac{1}{2}$ gr. or 0.008 to 0.03 gm.

8. *Spinocain*.—Contains novocaine, 0.2 gm., strychnine sulph. 2.2 mg., in $14\frac{1}{2}$ p.c. alcohol in normal saline 2 c.c. Also contains Gliadin which prevents diffusion in the subarachnoid space until the anæsthetic has been absorbed.

PHARMACOLOGY

Cocaine is a *general protoplasmic poison*, causing irritation and destruction of cells. It stops movements of leucocytes, amœbæ and ciliated cells. A 5 p.c. solution given subcutaneously may cause death of the tissues, producing either necrosis or a sterile abscess. For the same reason its application to the eye may result in cloudiness or ulceration of the cornea, but this is not ordinarily observed.

Locally.—Cocaine hydrochloride is the strongest and the most soluble of all preparations. It has no action on the unbroken skin, although a ten per cent. ointment may produce a demonstrable depression of sensation, but no true local anæsthesia (Clark). Applied to the mucous membrane or injected subcutaneously it causes blanching by constricting the local blood vessels and stimulation of the vasoconstrictor nerve-endings, and anæsthesia from the paralysis of the sensory nerves. Injected subcutaneously it deadens the sensibility and reddens the part around the puncture. Since these effects are local it follows that the drug must be applied in sufficient concentration to reach the nerve supply of the part which it is desired to influence. Although the sense of pain is abolished, the sense of touch is not so readily lost, and the temperature sense is scarcely affected, if at all. If the solution is made alkaline by the addition of sodium bicarbonate its efficacy is increased 2 or 4 times, due to easier penetration of the free anæsthetic base as compared with its salts, specially when injected into nerve trunks, and probably for subdural injection and on application to mucous surfaces (Sollmann). These effects may be produced by a 5 to 10 p.c. solution in about one to four minutes, and will last from fifteen minutes to an hour. The period however depends upon the concentration of the solution used and the vascularity of the part. Its action is prolonged and intensified by the addition of adrenaline,

which still further constricts the vessels and prevents its rapid removal by the circulation (*see* Adrenaline).

Injected along the trunk of a mixed nerve it paralyses the sensory fibres and abolishes pain of the area supplied by that nerve. This method of producing anæsthesia is known as "nerve blocking" or "regional anæsthesia." Injected intrathecally by lumbar puncture it abolishes sensation below the umbilicus though the power of movement remains unimpaired. Cocaine possibly acts on the posterior nerve roots. This method of anæsthesia is adopted for the production of "intraspinal anæsthesia."

Internally. **Mouth**—Locally applied it abolishes the sensibility and sensation of tastes of the tongue, and sensibility of the palate and fauces. It diminishes the salivary secretion.

Stomach and intestine.—In very minute doses it acts as a stomachic tonic, and in moderate doses diminishes the flow of the gastric juice, and deadens the sensation of hunger and of pain, if present. The same anæsthetic action is also noticed here, and cocaine therefore stops vomiting. In experimental works with strips of intestine, cocaine augments their movements. This effect is due to the direct action of the drug on the muscles. In large doses it checks peristaltic action.

Heart and circulation.—After a momentary slowing the heart beats faster. This effect was at one time thought to be due to paralysis of the vagus, but since the stimulation of the vagus slows the heart even in late poisoning, the acceleration must be due either to its direct action on the muscle or stimulation of the accelerator mechanism. After large doses the heart becomes weak and slow either from direct muscular depression or vagus stimulation, and death may take place from cardiac failure. In the earlier stages of poisoning the blood-pressure rises considerably from stimulation of the vaso-constrictor centre together with the increased rate of the heart. The pressure subsequently falls. As already noted cocaine causes constriction of vessels when locally applied, but no such effect is observed in general poisoning as it does not circulate in sufficient concentration to produce the effect as that would be fatal to the heart and respiration.

Respiratory tract.—Topically applied it deadens the sensibility of the nasal mucous membrane. Given internally it first increases the respiratory movements from the stimulation of the respiratory centre but soon depresses them. During the spasms it becomes irregular and assumes a Cheyne-Stokes type. Death results from asphyxia due to respiratory failure.

Nervous system. *Cerebrum.*—Cocaine stimulates the entire central nervous system, and in small doses it increases

the higher functions of the brain, while in man there is some psychic stimulation and wakefulness (caffeine action). In large doses it acts like atropine producing talkativeness and cheerfulness, and a feeling of comfort and ease with the abolition of mental and bodily fatigue. For these effects coca leaves are largely used by the people of Peru and Bolivia. All observers agree that it increases muscular work and possibly like caffeine increases mental powers when taken in small quantities. Often it causes sleeplessness though without much discomfort. The respiratory, vasomotor and accelerator centres and the motor areas of the brain are stimulated, and there is a tendency to motor activity and restlessness. These effects are central, and therefore are antagonistic to opium. Larger doses induce convulsions, which are not of spinal origin, but produced by some action on some undetermined part of the hind brain. At an earlier stage the medulla is affected when the respiration is quickened with evidence of reflex excitability which in toxic doses may become so exaggerated as to cause convulsions like strychnine. Cocaine first stimulates the brain, then the midbrain and medulla, and finally the cord, the action being one of descending stimulation. In other words with small doses the symptoms arise from the brain, but as the dose is increased those from the lower part of the nervous system become manifest. This stimulation is followed by depression, first affecting the cerebrum, then the bulb and lastly the cord.

Eye.—A 4 p.c. solution dropped into the eye causes complete anæsthesia of the conjunctiva and cornea and partial anæsthesia of the iris, dilatation of the pupil, exophthalmos and vaso-constriction. It partially impairs the range of accommodation but the light reflex is not lost. The dilatation is not maximum, since atropine causes a further dilatation when applied to a cocainised eye. These effects have been attributed to the stimulation of the sympathetic nerve-endings, and as they are more quickly produced when the drug is applied topically than when taken by the mouth, they appear to be due to direct local action. On the other hand some hold that dilatation is caused by the weakening of the circular fibres of the iris, much in the same way as other unstriated muscles are affected. The oculomotor endings are not affected unless strong solutions are used when there is some impairment of accommodation. It slightly lowers the intra-ocular tension due to vaso-constriction, but this effect is not constant.

Metabolism is not much altered. The temperature rises in cocaine poisoning, due essentially to increased heat production from muscular excitement.

Elimination.—It is eliminated in the urine, the quantity of which is increased *pari passu* with dilatation of the vessels

of the kidneys, although at first they are contracted when the secretion is diminished. A portion is excreted *via* the liver while a small quantity is retained in the tissues and eliminated slowly so that cocaine may be cumulative after repeated doses.

Acute toxic action.—Acute poisoning is not infrequent. Susceptibility varies due partly to uncertainty of absorption and partly to rapid destruction and idiosyncrasy. Ordinary fatal dose is 18 grs., though death may take place from $\frac{1}{2}$ gr. Toxic symptoms have been produced from a hypodermic injection of $\frac{1}{4}$ gr. Waking hallucination like those in poisoning by Indian hemp, leading sometimes to mania, vertigo, occasionally dryness of the throat, respiratory and cardiac difficulty, cramps in the limbs, inability to move, and a sensation of foreign bodies, such as pebbles or worms, especially the latter moving under the skin, are characteristic. Pupils dilate and reflexes are exaggerated. After very large doses epileptiform convulsions accompanied by circulatory and respiratory depression occur. Death takes place through failure of respiratory centre or collapse with very low blood-pressure.

Treatment.—As a preventive during local anæsthesia previous use of sedatives like barbiturates half an hour before by the mouth diminishes risk. Adrenaline or ephedrine hypodermically in spinal anæsthesia. In *poisoning*, luminal sodium or amytal sodium for convulsion, or paraldehyde. For collapse, adrenaline $\frac{1}{2}$ c.c. with saline. Artificial respiration.

Chronic toxic action or "Cocainism."—Like coca craving, cocaineomania is developed either in shaking off morphine or alcohol habit or from the temporary use of cocaine as a stimulant. Cocaine habit is rapidly increasing notwithstanding law against the sale of this drug. It is more dangerous to the health and moral than opium, and its habit increases sexual desire in both men and women, and also causes perverted sexual passion. It is taken with prepared *pan* in India, but as a snuff in other countries, which causes irritation of the nasal mucous membrane with perforation of the nasal septum. Disordered digestion, emaciation, giddiness, quick pulse, insomnia, dilated pupil visual or other hallucination, amnesia and impotence are prominent symptoms. Habitués may consume up to 10 or sometimes 20 to 30 grs. Total abstinence from the drug, strong coffee, nux vomica, and other tonics, change of air, etc., remove this pernicious habit.

THERAPEUTICS

Externally.—Cocaine is chiefly used as a *local anæsthetic* :—

Eye—Cocaine is largely used in ophthalmic practice as an anæsthetic during operation, for relief of pain, and as an astringent to constrict the vessels of the iris in inflammatory conditions. A 1 to 2 p.c. solution will allay pain, while a 4 p.c. solution or the official lamel dropped on the conjunctiva every three minutes 3 to 5 times, so far removes the sensibility as to enable the surgeon to perform many operations, as for example, cataract, etc., painlessly. Where iridectomy is necessary, a drop of the solution should be applied to the exposed iris immediately before making the section. Photophobia, conjunctival and corneal pain are soon relieved by the same collyrium. Combined with atropine sulphate cocaine has been found very efficacious in iritis and in many

painful inflammatory affections of the cornea. By adding $\frac{1}{2}$ gr. of pilocarpine nitrate to 1 dr. of a 4 p.c. solution, we can anæsthetise the eye without affecting the accommodation.

Nose, ear, anus, vagina, etc.—A 5 to 10 p.c. solution removes the sensibility of the mucous membrane of the nose, internal meatus of the ear, vagina, urethra and rectum, so as to allow small operations to be performed painlessly. The nasal irritation in hay fever, anal and labial pruritus, ear-ache, and the pain of anal fissure or ulcer are all relieved by the local application of cocaine.

Skin.—Although cocaine is known not to be absorbed by the intact skin, yet the application of the alkaloid combined with lard or oil allays the burning and pain of eczema, erysipelas, urticaria, sore nipples, etc. The pain and irritation of burns and scalds are soon relieved, if the part is first brushed over with a 4 p.c. aqueous solution of cocaine hydrochloride and then the pure alkaloid combined either with carron oil or with paraffin or boric acid ointment is applied. A hypodermic injection of cocaine removes the pain of scorpion-stings. Buboës, small tumours, inflamed bursæ and small abscesses may be painlessly dealt with after injection of cocaine in their neighbourhood. Many superficial neuralgias may be relieved by the local application of the alkaloid in oil of cloves, and sciatica by the injection of an aqueous solution into the sheath of the nerve.

Internally. Gums and teeth.—Cocaine, preferably the alkaloid, as it is less likely to be washed away by the saliva, is largely employed in dentistry to deaden the sensibility of the exposed pulp. Cocaine hydrochloride 1, chloral hydrate 5, and camphor 5, form an oily liquid when warmed which removes toothache. A tooth may be painlessly extracted by injecting a solution into the gums at its base, but this is a risky procedure. The mere rubbing of cocaine over the gums deadens their sensibility to such an extent as to annul the pain of the first application of the forceps.

Throat and larynx.—By applying a 20 p.c. solution to the soft palate and pharynx, enlarged tonsils or small growths in those parts may be excised, or the galvanocautery applied painlessly. By the same method the larynx may be explored and minor operations performed there without spasm or pain.

In painful sore-throat cocaine and rhatany lozenges give great relief by acting locally.

Stomach.—For its local effects on the gastric mucous membrane, it may sometimes be used in sea-sickness and vomiting of pregnancy. $\frac{1}{2}$ gr. with 15 ms. of glycerin in 1 dr. of water may be given every hour for this purpose.

USES OF LOCAL ANÆSTHETICS IN MAJOR OPERATIONS

Intraspinal anæsthesia.—By the direct application to the spinal cord of local anæsthetic drugs the passage of both afferent and

efferent impulses along the spinal roots may be blocked. The drugs commonly used for the purpose are stovaine (amylocaine hydrochloride), novocaine (procaine hydrochloride) and percaïne. Cocaine is not used as being too dangerous, and novocaine and percaïne have almost replaced stovaine. For injection into the lumbar region the following doses have been recommended by Jonnescu, viz.—stovaine 0.002 grm. ($\frac{1}{50}$ gr) with strychnine hydrochloride 0.001-0.002 grm. ($\frac{1}{60}$ to $\frac{1}{30}$ gr.). For cervical and dorsal regions 0.005-0.02 grm. ($\frac{1}{20}$ to $\frac{1}{5}$ gr.) and 0.0005-0.001 grm. ($\frac{1}{200}$ to $\frac{1}{100}$ gr.) respectively.

Sterilised solutions of stovaine are supplied in ampoules ready for use, and are put up in two forms. The *heavy solution* contains 5 p.c. of stovaine combined with glucose, each ampoule holding 2 c.c. When introduced into the thecal canal, the solution, owing to its specific gravity, assumes a position which can be varied by tilting the patient's spine, thus adjusting the level of the analgesia to some extent. To prevent the anæsthetic solution reaching the higher nerve centres, or from acting on the root of the phrenic or other respiratory nerves, the head and the shoulders must be kept at a higher level raised on pillows. Since the drug gets fixed in about 10 minutes the position may be altered after this period. The *light solution* is a 10 p.c. solution and is put up in ampoules of 1 c.c. in normal saline. It has the same specific gravity as the cerebro-spinal fluid, and is unaffected by gravitation. With this solution the patient may at once be placed on Trendelenburg position, whereas with the heavy solution it can only be done after the drug gets fixed in the tissues, i.e. after ten minutes which implies some waste of time.

A form of spinal analgesia extensively used in the Continent and America is by injecting the anæsthetic into the small layer of the loose tissue outside the dura. This method is allied to sacral analgesia.

But all these drugs have the drawback of being effective only in fairly concentrated solution and spreading towards the head by gravitational diffusion when a Trendelenburg position is adopted during operation necessary to maintain blood-pressure. The introduction of percaïne has altered the position. Although highly toxic it can be used in very high dilutions. Ampoules containing 20 c.c. of 1 in 1500 solution in 0.5 p.c. saline ready for use are available. As the solution is lighter than the cerebro-spinal fluid, the patient should lie on his face with his buttocks slightly raised for at least five minutes. This enables the solution to reach the posterior nerve roots. An injection of ephedrine or adrenaline is given at the same time to combat any fall of blood-pressure.

Spinal anæsthesia should be confined to operations below the nipple line, though claims have been made that anæsthesia can be induced as high up as the head, and such operations as enucleation of the tonsils have been performed. But unless undertaken by very expert hands this may lead to dangerous paralysis of the respiratory centre with fatal result. It is an ideal method for gynaecological operations, and for operations upon the rectum and bladder, and in diabetics. It is specially useful for persons who have a dread for chloroform or ether, or for losing consciousness. Since it blocks the nervous paths of shock impulses, it is an ideal anæsthetic for cases where shock from operation is anticipated, but should be avoided where the nervous shock is already present.

A frequent complication is retching and vomiting which makes abdominal operation rather disturbing. Failure of respiration sometimes gives rise to grave anxiety. This at one time was thought to be due to direct action on the centre but is now supposed to be indirect through insufficient blood supply from excessive fall of blood-pressure. The condition should be treated with oxygen, or oxygen and CO₂ 5 p.c. Some fall of blood-pressure is always present and this is not of any consequence.

Injection into the nerve sheath (intraneural) is used when a

permanent effect is desired as into the cut nerves in amputation stumps.

Anæsthesia by the local infiltration method consists in subcutaneous injection of either 0.1 p.c. of cocaine, or 0.24 p.c. of eucaine with 0.8 p.c. of sodium chloride, along the proposed lines of incision, and then into the deeper parts before cutting them. Nowadays cocaine is rarely used for the purpose, as it produces toxic symptoms, and novocaine is widely used, which in suitable doses is free from any toxicity, moreover the solution can be sterilised by boiling. As it does not constrict the arterioles, a little adrenaline chloride solution (0.002 to 0.005 p.c.) is added to check hæmorrhage, to prolong the period of anæsthesia and to reduce toxicity. The strength of the solution is 0.25 to 1 p.c. and the usual procedure is to start by raising on the skin over the required area a number of wheals by injecting the solution endermically. After a number of these wheals have been formed insert the needle deep into the tissues. In this way quite a large area can be made anæsthetic, and if necessary can be extended to deeper tissues by subsequent injections.

Regional anæsthesia.—In this the anæsthetic is used to block the passage of pain impulses by exposing the sensory nerve trunks to the anæsthetic solution leaving the nerve endings unchanged, so that sensation of pain does not reach the central nervous system. After a preliminary local anæsthesia the drug is injected into the nerve trunk or around it to cause a temporary sensory and motor paralysis. Novocaine is the drug of choice and a 2 p.c. solution is used. In the infiltration anæsthesia, the actual nerve-endings of the part to be operated upon are anæsthetised.

Regional anæsthesia has been largely used, and with much success, in gastric surgery by blocking the greater and lesser splanchnic nerves by infiltrating the loose retro-peritoneal tissue around the celiac plexus with a 5 p.c. solution of novocaine and adrenaline. By this method the stomach, small intestine, omentum, liver and hilus of the spleen can be sufficiently anæsthetised to be handled painlessly. The abdominal wall and parietal peritoneum are previously anæsthetised by the local infiltration method.

Toxic effects of local anæsthetics.—Quite a large number of operations are now performed with the aid of local anæsthetics, and since this entails the use of these drugs in large doses their toxic effects should be carefully noted. It should be remembered that local anæsthetics are protoplasmic poisons possessing special affinity for nerve tissue, injections of large amounts in solution will naturally affect the brain and the vital centres. The symptoms of overdosage are excitement, restlessness, deep and rapid breathing, dilated pupil, and feeble pulse. These are followed in severe cases by unconsciousness, convulsions and death. According to Farr intravenous lethal dose of a local anæsthetic is one-tenth of its subcutaneous lethal dose. Accidental introduction into a vein therefore is responsible for most of the cases of sudden collapse and death. Adrenaline increases the liability to cardiac failure by causing fibrillation of the ventricle as happens after chloroform anæsthesia.

In spinal anæsthesia cocaine is much too toxic and its use has been given up. Some patients have special idiosyncrasy to cocaine and death has occurred from mere application of small amount to mucous surface (Ross and Fairlie). The use of cocaine and butyn should be restricted to surface application, and the total quantity of cocaine should not exceed 1 to 1½ grs. The chief danger of endo-thelial injection is fall of blood pressure and it is believed that this depends upon the number of constrictor fibres paralysed by the injection.

Novocaine is considered to be the safest. Given subcutaneously the total quantity should not exceed 0.2 grm. when used in 2 p.c.

solution. It is better not to exceed a concentration of more than 1 p.c. It injures the kidney and may cause albuminuria.

After-effects.—Apart from the after-effects seen after general anaesthesia, severe headache is a common trouble and has been attributed to increased intracranial pressure. It is occipital or sub-occipital and may be aggravated by raising the head. Some temporary relief is obtained by lumbar puncture. Mild cases yield to ordinary treatment. In severe forms, hypertonic saline infusion or an intravenous injection of glucose and saline (50 p.c. glucose), or 2 c.c. of 50 p.c. magnesium sulphate are useful.

Transient paralysis of the sphincters of the bladder, or squint may appear, which disappear within a few weeks.

The following are the disadvantages of using cocaine:—

1. Its general poisonous action.
2. Growth of fungus on keeping
3. Its tendency to formation of vicious habit.
4. It is destroyed by boiling.

Contra-indications.—The chief contra-indication to the injection of local anaesthetics is the presence of sepsis. As full consciousness is retained during the operation, it is unsuitable for children and highly nervous adults. They are best treated under general anaesthetics. In debilitated patients the vitality of the tissues may be unable to withstand the increased pressure of the injection and sloughing may result.

Benzocaine was introduced under the name of *Anæsthesine*. It is insoluble in water but fairly soluble in oil, and is largely used as a surface anaesthetic in the form of dusting powder mixed with starch or talc powder in the proportion of 10 to 15 p.c., in burns, ulcers, eczema, etc. It may also be used as an ointment (10 p.c.). As a suppository (10 gr.) it may be used in painful and inflamed piles.

Procaine hydrochloride or *Novocaine* has a wide field of usefulness and has replaced cocaine in injection anaesthesia as it is less toxic and less irritating, but the effects are less prolonged. Since it is absorbed with difficulty from mucous surfaces it cannot reduce pain when applied to the conjunctiva, nose, or urethra. It does not constrict the vessels, rather dilates them, and therefore it is usually combined with adrenaline which makes it less toxic by diminishing absorption and prolongs its effects. The usual strength for injection is 0.5 to 2.0 p.c. The solution can be sterilised by boiling. For the production of regional or infiltration anaesthesia it is largely used in place of cocaine. For extensive infiltration, 300 c.c. of 0.5 p.c. solution may safely be used; for nerve block 100 c.c. of a 2 p.c. solution are recommended but in actual practice such large quantities are not required.

Amylocaine hydrochloride or *Stovaine* is slightly less toxic than cocaine and is preferred for intraspinal anaesthesia. It is however slightly more toxic than novocaine. It is an irritant and causes hyperæmia, does not constrict vessels nor cause dilatation of the pupils.

Orthocaine is largely used as a local anaesthetic to abraded and mucous surfaces and is used for its local effect to relieve gastric pain, in ulcers, simple or malignant, in 1 to 2 gr. doses, and as a dusting powder or as an ointment (10 p.c. in simple ointment) to relieve pain in burns, ulcers, etc. It has the drawback of producing severe irritation and even necrosis.

PERCAINE. (*Not official*). *Syn*—Nupercaine—Hydrochloride of *a*-butyl oxy-cinchoninic acid diethylethelenediamide. In odourless, tasteless crystals, readily soluble in water forming a neutral solution.

Dose— $\frac{1}{4}$ to $1\frac{1}{2}$ gr. or 0.05 to 0.1 grm

ACTION AND USES

Percaine differs from the above group in being a derivative of quinoline, a group of substances not used as local anaesthetic. It is

soon decomposed by the presence of a trace of alkali, and must be kept in alkali-free glass containers, and syringes, needles, etc., must be boiled in water free from any alkali and should not come in contact with tap water or Ringer's solution. The drug was introduced by Karl Meischer and since then it has profoundly modified the technique of spinal analgesia. It is a much more powerful local anæsthetic than either cocaine or novocaine and is about twenty-five times more toxic than novocaine and three times than cocaine, but this is offset by the fact that its minimal effective concentration is about one-fortieth. It is also extremely effective for surface application, and has a more prolonged action than cocaine. A dilution of 1 in 125,000 has a demonstrable effect on rabbit's cornea, whereas it requires 1 in 10,000 to produce the same effect with cocaine. Although it is largely used for spinal anæsthesia symptoms of poisoning were observed after excessive doses, viz. clonic convulsion, irregularity of the heart, circulatory failure, cyanosis and respiratory paralysis.

For *local anæsthesia* to mucous surface a 1 to 2 p.c. solution with a few drops of 1 in 1000 adrenaline is sufficient. For *infiltration anæsthesia* the strength is 0.5 to 1 in 1000, with the addition of 10 to 20 drops of 1 in 1000 adrenaline solution for every 100 c.c. of anæsthetic. For *spinal anæsthesia* a 1 in 1500 solution in 0.5 p.c. saline is used, and of this 6 to 18 c.c. are required.

Sterile solutions of 20 c.c. ampoules of 1 in 1500 in 0.5 p.c. saline are available.

It has the following advantages over novocaine:—

1. It is a powerful anæsthetic to mucous surfaces.
2. When given by injection the effects last for several hours, while with novocaine they last only for half to one hour.
3. The minimum effective concentration is so small that for all practical purposes it has no toxicity.
4. There is less fall of blood pressure and therefore less shock.

In the following table the differences in the action of cocaine, amylocaine, procaine and benzamine lactate have been summarised.

	Cocaine	Amylocaine or Stovaine	Procaine or Novocaine	Benzamine Lactate
Toxicity	Highest	$\frac{2}{3}$ of cocaine but more than procaine	Low, $\frac{1}{3}$ to $\frac{1}{4}$ of cocaine	$\frac{1}{2}$ of cocaine
Irritation and tissue injury	Non-irritant in ordinary concentration	Irritant in high concentration	Non-irritant	Smarting pain
Vaso-constriction	Yes	Dilates vessels	Dilates vessels	Nil
With adrenaline	Prolongs effect	Interferes vaso-constriction	Vaso-constriction. Acts efficiently	Interferes its effect
Stability of solution	Slowly deteriorates. Should be freshly made	Keeps well, but destroyed by trace of alkali	Keeps well but gets discoloured	Keeps well
Sterilisation	Destroyed by boiling. Can be brought to boiling point	Can be boiled	Can be boiled	Can be boiled
Pupil	Dilates	Nil	Nil	Nil
Surface anæsthesia	Efficient	Not efficient	Not efficient	Nil
Uses	Useful for surface anæsthesia with adrenaline	With strychnine for spinal anæsthesia; also for infiltration anæsthesia	Useless for surface anæsthesia. Useful for spinal and infiltration anæsthesia	Useful for infiltration anæsthesia

GROUP VI

DRUGS ACTING ON THE CARDIO-VASCULAR SYSTEM

Class A Drugs acting on the heart

- 1 Cardiac tonics
Digitalis, Strophanthus, Squill, Apocynum
- 2 Cardiac depressants
Aconite, Acid Hydrocyanic Dilute

Class B Drugs acting on the vessels

1. Drugs raising the blood-pressure (Vaso-constrictors)
Adrenaline, Ephedrine, Benzedrine, Pituitary Extract, Ergot
2. Drugs lowering the blood-pressure
(a) Vaso-dilators Amyl Nitrite, Nitro-glycerin, Erythrol Tetranitrate,
Sodium Nitrite, Spirit of Nitrous Ether (*see* Diuretics), Acetyl-choline
(*see* page 233)
(b) Measures reducing the volume of blood Leech, Bloodletting

CLASS A: Drugs acting on the Heart

The heart is a peculiarly constructed nervo-muscular organ performing complex functions. It is capable of originating spontaneous rhythmical movements. The theory that these movements are due to the ganglia located in the heart is no longer believed, but evidence goes to prove that they originate from the spontaneous impulses generated in the muscle itself—myogenic—and Gaskell describes as its functions, *rhythmicity, excitability, contractility, conductivity* and *tonicity*.

By virtue of the excitability the heart muscle responds to external stimuli by producing contraction. But unlike other muscles it will not contract when the stimulus is too weak, but if the stimulus is adequate the muscle will contract to its full ability, *i.e.* all or none. Unlike skeletal muscle the cardiac muscle will not respond to stimuli during the phase of contraction and this period during which the heart will not contract is known as the "refractory period." Conductivity is another property of the cardiac muscle, this is specially developed in the bundle of His and its branches. Drugs which depress conductivity also diminish excitability.

Though the muscular fibres spontaneously contract yet they can be controlled and regulated by the nerve centres. Two centres control the cardiac mechanism, *viz.*, the cardio-inhibitor and the accelerator. Afferent impressions from various parts of the body, including the seat of mind and the heart, are transmitted to the centres in the medulla to be reflected to the heart. The vagus system consists of the centre, nerves, ganglia and nerve-endings, the chief function so far as the heart is concerned is that of restraint or inhibition. It begins at the centre whence the fibres pass to groups of cells in the heart-wall forming vagus ganglia, whence fibrils pass to the sino-auricular node (normal pace maker) in the auricle and to the bundle of His. Stimulation of any part of this system is followed by slowing or weakening of the heart beat with depression of conductivity and loss of tone, either by acting on the auriculo-ventricular bundle or by diminishing the irritability of the ventricle itself, or tonicity; while depression results in increased frequency and strength of the beat and increased tone by making the heart free of the vagus influence. The accelerator nerves belong to the sympathetic system, and consist of centre, nerves, ganglia and nerve-endings. The effect of excitation, besides increasing the rate, is to increase the force of contraction and conductivity. The vagi (parasympathetic) and accelerators (sympathetic) are therefore antagonistic in their effects, and since they are in constant activity they form a sensitive balanced control mechanism which favour prompt response to any influence.

The contraction of the heart is initiated in the sino-auricular node situated at the mouth of superior vena cava. From here the wave passes over both the auricles to the auriculo-ventricular node, which is situated between the auricles and the ventricles. From the auriculo-ventricular node the wave passes down the bundle of His to the endocardial surface of both ventricles. The bundle and its branches are composed of large fibres, which are termed Purkinje fibres.

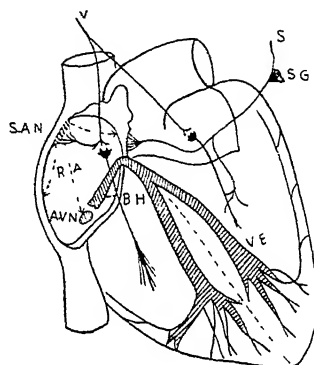


Fig 7.—Innervation of the Heart S.A.N., sino-auricular node A.V.N., auriculo-ventricular node B.H., bundle of His dividing into two branches; one entering the right, the other left ventricle. V., parasympathetic fibres (vagus) terminating round the ganglion cells in the auricles. V.E., vagal endings in the auricles and ventricles S., sympathetic terminating round the stellate ganglion (S.G.), and the nerve fibres issuing from the ganglion end in auricles and ventricles

(Modified from Wright's Applied Physiology)

In order that the heart may functionate properly it must have ample supply of oxygen. Under normal conditions weight for weight this oxygen consumption is greater than any other tissue of the body. It receives oxygen from the coronary arteries and the efficiency of coronary circulation depends upon the heart's contraction. As long as the supply of oxygen is adequate the heart can utilise both carbohydrate and protein to supply heat and energy, and any decrease in oxygen will enable the heart to utilise glycogen to a limited amount which it reduces to lactic acid, but is rapidly poisoned by it. Therefore any interference with coronary circulation at once injures the heart, and other things being equal slowing of the heart ensures better coronary circulation resulting in improved nutrition and recuperation.

The coronary arteries are supplied by the sympathetic and the parasympathetic vagus. The stimulation of the former dilates and that of the latter constricts the vessels. It follows therefore that both the blood supply to the heart and consequently its work are diminished by vagus stimulation and increased by sympathetic stimulation.

The maintenance of efficient circulation depends upon the condition of the heart muscle. Normally the different parts of the entire circulatory system are so adjusted that they facilitate the work of the heart, and any disturbance in any part of the circulatory chain entails extra work upon the heart muscle which asserts itself to meet the requirements of the body.

Two conditions intimately associated with heart disease require special mention, *viz.* "compensation" and "auricular fibrillation."

Compensation.—The term is used to designate the degree of impairment of heart's activity, *i.e.* the ability of the heart to maintain efficient circulation against some leakage or other adverse condition. We speak of failure of compensation or heart failure, when the heart is unable to maintain it. This inability is due to excessive strain on the heart muscle. For practical purposes Mackenzie differentiates two functions of the heart muscle. The one necessary to maintain efficient circulation when the body is at rest, which he calls "rest force," and the other called into action during an effort, however small, which he calls "reserve force." The first signs of heart failure are observed with the exhaustion of the reserve force, and if the strain continues without any repair or recuperation, true signs of heart failure appear, when the heart muscle is unable to maintain efficient circulation even during the period of rest. The signs of failure of compensation are dyspnoea, orthopnoea, weak and dilated heart, rapid pulse, sluggish peripheral circulation with cold extremities, oedema and dropsy.

Auricular flutter and fibrillation.—These terms are applied to two forms of disordered heart's action characterised by extremely rapid auricular beats. This is observed by electro-cardiogram tracings. In fibrillation the auricular waves are irregular and have a rate of about 400 to 500 per minute. In flutter the waves are regular and have a rate of 250 to 300 per minute. In these conditions the bundle of His is incapable of conducting impulses at such rates and a variable degree of heart block is always present so that the ventricular rate is about 100 to 150 per minute. In fibrillation there is complete irregularity of the pulse—no two beats being the same in force or rhythm—and absence of signs of auricular contraction. It is a serious complication, and occurs in almost all cases of heart failure and in old standing cases of mitral disease.

Normally the wave of excitation originated at the sino-auricular node is followed by a refractory period, and the whole auricle remains in that condition till the wave is completed. In fibrillation the refractory period is shortened and the wave of excitation becomes slow so that by the time the waves have travelled over the auricle another part recovers (owing to shorter refractory period) and sends waves of excitation before the previous ones have completed. Thus innumerable waves of excitation arise from abnormal parts of the auricle and travel round and round producing what has been termed by Lewis "circus movements." These irregular impulses pass into the ventricles which respond irregularly and inefficiently at a rate far greater than their maximum capacity. As a consequence of this the ventricular muscles become exhausted. Digitalis and quinidine are very useful in this condition.

Heart rate—The rate of the heart may be affected in the following ways :—

A. Slowing of the rate may be caused

(a) *By acting on the vagal centre.*—Drugs which stimulate the central nervous system also stimulate the cardiac centre. But the effect on the vagal centre is more powerful than on the sympathetic, so that slowing of the heart results. The best example of stimulation of the vagal centre is deficiency of the oxygen in the blood as happens in asphyxia. Aconite, digitalis, strophanthus, squill, convallaria, picrotoxin, strychnine and morphine cause slowing by stimulation of the vagal centre. High blood-pressure affects the medulla and causes slowing of the heart, and any cause which will raise the blood-pressure will produce slowing. This effect is only observed when the vagi are intact or not paralysed by atropine. Thus adrenaline produces slowing during the period when the pressure is highest, although it has no direct effect on the medulla. High blood pressure distends the aorta and the carotid sinus which send afferent impulses to the cardiac centre and reflexly slows the heart. Pituitary extract

also acts in the same way. Afferent impulses through the 5th and the 10th nerves reflexly stimulate the vagal centre, e.g. inhalation of ammonia vapour.

(b) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium stimulate the ganglion cells in the course of the vagus and cause slowing. These are depressed subsequently and in large doses paralysed when the rate is accelerated.

(c) *By acting on the nerve-endings.*—Stimulation of the endings of the parasympathetic (vagus) causes slowing of the rate; e.g. by pilocarpine, acetyl-choline, physostigmine, and members of the digitalis group.

(d) *By acting on the muscle.*—Drugs alter the rate of the heart by their action on the muscle. Many drugs in small doses cause slowing, while in large doses produce quickening through their effects on the excito-motor portion of the heart (bundle of His). Barium, digitalis, quinidine, aconite and pituitary extract cause slowing by acting directly on the cardiac muscle.

B. Quickening of the rate may be caused

(a) *By acting on the sympathetic centre.*—Very little is known regarding the action of drugs on the accelerator centre. Cocaine stimulates the centre and causes acceleration of the heart. Excitement and anoxæmia increase the frequency of the heart's rate either by stimulating the sympathetic centre in the medulla or by stimulating the secretion of adrenaline.

Reflex stimulation, as by the application of counter-irritants, accelerates the heart, and any cause which lowers the blood pressure causes quickening of the heart by diminishing the tonus of the medulla.

(b) *By acting on the nerve-endings.*—Atropine, hyoscyamine and hyoscyne cause quickening by paralysing the vagal nerve-endings, while adrenaline, tyramine, ephedrine, cocaine and pilocarpine in small doses cause acceleration by stimulating the sympathetic nerve-endings.

(c) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium cause acceleration in large doses by paralysing the ganglion cells in the course of the vagus.

(d) *By acting on the muscle.*—Caffeine, digitalis in poisonous doses.

1. Cardiac Tonics

DIGITALIS FOLIUM

Digitalis Leaf. (Digit. Fol.)

Source—Leaf of *Digitalis purpurea*, rapidly dried at a temperature between 55° and 60° as soon as possible after collection.

Characters.—From 10 to 30 cm. or more in length, up to 4 to 10 cm broad, with a winged petiole, ovate-lanceolate, subacute, crenate. Upper surface somewhat rugose, dull green, slightly hairy. Under surface paler, pubescent, with prominent veins. No odour. Taste, very bitter.

Composition—The chief active principles of digitalis are several *glycosides* which on hydrolysis split up into sugar and a non-sugar component, *aglucone*. The aglucones are responsible for the digitalis action, whereas the sugar helps penetration. They may be grouped into two classes, *viz* :—

(a) Alcohol soluble—

1. *Digitoxin*, crystalline, $C_{41}H_{64}O_{13}$, represents the digitalis action. It is the most abundant, active and most important constituent of the leaves (0.2 to 0.4 p.c.) It undergoes hydrolysis and forms aglucone, *digitoxigenin* and a sugar *digitoxose*.

2. *Gitoxin*, $C_{41}H_{64}O_{14}$, which also breaks up into *gitoxigenin* and sugar *digitoxose*.

3. *Digitalin*, amorphous, $C_{36}H_{56}O_{14}$. Occurs in leaves and seeds. Splits into dextrose, digitaligenin and digitalose. Produces typical digitalis effect, half as active as digitoxin.

(b) *Water soluble*.—

4. *Gitalin* and *digitaletm* are mixtures of indefinite composition.

5. *Digtonin*, a saponin, occurs both in crystalline and amorphous forms. The crystalline form is less readily soluble in water. It helps the solution of digitoxin in water.

6. *Digoxin*, $C_{41}H_{64}O_{14}$, found in *Digitalis lanata*. It hydrolyses into *Digitoxigenin* and *Digtoxose*.

OFFICIAL PREPARATIONS

1. *Digitalis Pulverata*. *Syn.*—*Powdered Digitalis*.—Leaf reduced to moderately coarse powder, no portion being rejected. Standardised by biological assay to contain 10 units in 1 gramme. 10 grs. contains 6 units of activity. B.P. Dose.— $\frac{1}{2}$ to $1\frac{1}{2}$ grs. or 0.03 to 0.1 gm. *For single dose*.—3 to 10 grs. or 0.2 to 0.6 gm.

2. *Infusum Digitalis Recens*.—Freshly prepared from powdered leaf. Should be used within 12 hours of preparation. One-twentieth the strength of tincture. 6 units of activity in 4 oz. B.P. Dose—90 to 300 ms. or 6 to 20 mls. *Single dose*—1 to 4 oz. or 30 to 120 mls.

3. *Tinctura Digitalis*.—No. 1 prepared from the leaf, and No. 2 from powdered leaf. Contains 6 units of activity in 90 ms. B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil. *For single dose*.—30 to 90 ms. or 2 to 6 mls

NON-OFFICIAL PREPARATIONS

1. *Digitalin*—Under this name the following varieties are found—

(a) *Amorphous Digitalin (Homolle)*—Consists of mixture of glycosides. Insoluble in water. *Dose*— $\frac{1}{100}$ to $\frac{1}{300}$ gr. in granules.

(b) *Crystallised Digitaline (Nativelle)*—Consists mostly of digitoxin. Is cumulative. *Dose*—Granules $\frac{1}{240}$ and $\frac{1}{1000}$ gr $\frac{1}{1000}$ gr = 16 ms of tincture or $1\frac{1}{2}$ gr. powdered leaf

2. *Digitoxin, B.P.C*—In minute, white crystals. *Dose*— $\frac{1}{1000}$ to $\frac{1}{500}$ gr or 0.0001 to 0.001 gr

3. *Digalen*.—Contains the active principles of the leaves 1 cc = 150 frog unit or 1 cat unit, i.e. 0.1 gm. *Digitalis pulverata*. One tablet or ampoule = $\frac{1}{2}$ cat unit or 0.05 gm *Digitalis pulverata*. *Dose*—5 to 15 ms or 0.3 to 1 mil.

4. *Digipuratum*—A purified solid extract. Contains the cardiac glycosides of the leaves in combination with tannin and freed from most of the inactive constituents. Obtainable in solution, tablets (0.1 gm) and ampoules

5. *Pilulæ Digitalis Co, B.P.C.* *Syn*—*Guy's Pill*—Powder digitalis, powder squill, pill of mercury, each 1 gr, syrup of liquid glucose q.s for one pill. *Dose*—1 to 2 pills

6. *Digoxin*—A crystalline glycoside obtained from *Digitalis lanata*. It is soluble in water and can be given *intravenously* in doses of $\frac{1}{120}$ to $\frac{1}{100}$ gr. or 0.0005 to 0.001 gm *For oral use*— $\frac{1}{100}$ to $\frac{1}{40}$ gr or 0.001 to 0.0015 gm *Maintenance dose*, $\frac{1}{240}$ gr or 0.00025 gm

PHARMACOLOGY

Locally.—Digitalis, owing to the presence of glycosides, powerfully irritates the mucous membrane and subcutaneous tissues causing inflammation and pain. This effect is more marked with digitoxin than with digitalin which is often used subcutaneously without causing any local irritation. Subcutaneous injection of digitoxin causes much pain and irritation and sometimes a sterile abscess.

Internally. Gastro-intestinal tract.—Small doses ap-

pear to have no action, but the glycosides and the saponins are sometimes irritating to the gastric mucous membrane. If continued long even in therapeutic doses it causes **nausea** and **vomiting**, due not to any local irritant effect on the stomach but to stimulation of the vomiting centre after absorption, or perhaps through stimulation of the sensory fibres of the vagus in the heart, which is a secondary manifestation of the cardiac action. In practice this should be regarded as a sign of over-digitalization. It is slowly absorbed from the intestine, and is not affected by the digestive juices, but in case of venous engorgement, as happens in diseases of the heart, absorption is delayed and there is some destruction of the glycoside. The tincture and digitoxin however are quite easily absorbed and will manifest their effect on the heart in from four to seven hours. According to Cloetta, digitoxin is more resistant to digestive juices than other glycosides. All the glycosides are readily absorbed when given per rectum.

Heart and circulation.—Digitalis produces its principal effects on the circulatory system. It slows the rate of the heart, prolongs the period of diastole, increases the force of contraction, and improves the tone of the muscle. Before proceeding to describe its action on the different structures of the heart it will be convenient to discuss its effects on the frog first, for it was in this animal that its effects on the heart were first studied. Although the effect of digitalis on the frog's heart is different to that on the mammalian heart it has been pointed out that the reaction of human heart in diseased condition approximates more closely to that of the frog's heart than to that of the mammalian organ (Cushny).

Frog.—If a tracing of the heart of a decerebrated frog is taken and then an injection of digitoxin is given, a well-defined series of phenomena are observed. The systole becomes more powerful and the heart becomes slower from prolongation of the diastole. The increased contraction enables the heart to empty itself more completely during the systole and the ventricles become more completely filled through prolonged diastole. If the dose is increased the auriculo-ventricular conductivity is lowered and the rhythm is altered. There may be two or more beats of the auricle for each ventricular contraction, or there may be a long pause in diastole between a series of regular contractions. Finally, the ventricles may stop beating and remain stand-still in the position of systole whilst the auricle continues to beat. It is obvious that two changes take place in the frog's heart, *viz.* (1) *change in rhythm*, and (2) *change in tone and contraction*. These effects are due to direct action of the drug on the cardiac muscle since the same effects can be elicited after destruction of the central nervous system,

or division of the vago-sympathetic fibres, or in the excised heart under atropine.

Mammals.—The action of digitalis on the mammalian heart may be divided into three stages depending on the preponderance of its effects either on the inhibitory mechanism or on the cardiac muscle.

The first or therapeutic stage is characterised by moderate slowing through stimulation of the vagus centre and increased contraction of the cardiac muscle resulting in more complete systole. The output of the heart is thus increased while the slowing gives more time for the ventricles to be better filled. As a result of this effect the veins empty themselves more thoroughly into the heart, the venous pressure falls and the arteries get better filled. The arterial pressure first rises owing to the increased ventricular force and greater output. If the dose is increased the arterioles contract from stimulation of the vaso-constrictor centre and from direct stimulation of the muscles of the vessels.

The second stage or that of poisoning is marked by over activity of the inhibitory mechanism and the pulse becomes slower and irregular. The heart gets more time to fill, consequently the output with each systole is greater than normal. But since the rate is extremely slowed the total output per minute and the efficiency of the pumping action of the heart is less than normal. Moreover owing to the inhibition of the conductivity of the muscles of the auriculo-ventricular bundle, the auricular impulses do not pass on to the ventricles, thus producing incipient or less frequently complete heart-block, *i.e.* the ventricles beat at a slower rate than the auricles, so that the number of beats of the heart and that of the pulse is different.

The third stage follows excessive doses and is hardly ever observed clinically in man. The heart muscle becomes extremely irritable and the ventricular rhythm becomes accelerated, but the nervous mechanism is not involved since the stimulation of the vagus may slow the rate. The auricular muscles are also affected and the combination of these effects gives rise to irregularity of the heart producing auricular-ventricular arrhythmia, spontaneous rhythm, extra-systole and finally fibrillation leading to failure of myocardium and the stoppage of the heart in diastole.

Digitalis produces all the above circulatory effects through its action on the following five structures :—

1. The sino-auricular node.
 2. The cardiac muscle.
 3. The auriculo-ventricular bundle.
 4. The coronary arteries.
 5. The systemic arteries.
1. By its inhibitory action on the sino-auricular node

it causes a slowing in the rate of the heart. This effect is not so marked in therapeutic doses but is observed in toxic doses and may not be due entirely to digitalis action on the sinus node, but in part to stimulation of the vagus centre. Since very little slowing is observed after cutting the vagi or in an isolated heart, it is evident that this slowing is not due to its action on the ending in the sinus node but is the result of stimulation of the vagal centre. This slowing is often a desirable therapeutic effect, but in certain conditions, *viz.*, old age, cardio-sclerosis, and in some infectious fevers, therapeutic doses of digitalis fail to effect any such slowing. A second effect of digitalis on this node is to interfere with the regular rhythmic projection of impulses, so that a sinus arrhythmia is set up, *i.e.* the heart-rate shows regular alternating short phases of acceleration and slowing. This effect is also due to stimulation of the vagus, and is checked by atropine or section of the vagi.

2. Digitalis acts directly on the cardiac muscle, and its effect here is threefold, *viz.*—(1) it increases its tonicity, *i.e.* the heart remains in a state of partial contraction or incomplete relaxation during the period of diastole; this effect keeps the heart in readiness to respond at once to stimulation; (2) it increases its contractility; and (3) it renders it more irritable, *i.e.* increases its sensitiveness to stimuli. The papillary muscles are also toned and strengthened. The first two effects—increase of tone and contractility—are of great value in all cases of cardiac failure, but the third effect—*irritability*—if increased beyond the normal, as may happen in toxic doses, may give rise to harmful symptoms such as premature contractions, tachycardia, and fibrillation. By increasing the excitability of the ventricular muscle, digitalis may cause further increase in the rate of fibrillation, or an increase of ventricular beats in cases of complete heart block.

Another important effect of digitalis, as observed in electro-cardiogram, is an alteration in the T waves which becomes inverted, and since this effect is not abolished by the previous use of atropine it must be due to its direct action on the muscle.

In therapeutic doses the rhythm of the heart becomes slower, the ventricles contract and become smaller and empty themselves more thoroughly than they normally do, so that with each beat the ventricles expel more blood into the aorta and pulmonary arteries. The ventricular changes under digitalis consist in reducing the number of beats and increasing the relaxation of the fibres from inhibitory activity, and strengthening the systole from direct action on the muscle, which also limits the period of relaxation without affecting the rhythm.

3. The function of the auriculo-ventricular bundle is to conduct impulses from the auricle to the ventricle, so that the ventricular contraction follows the auricular one regularly, and the time taken for the passage of the impulse down this bundle (A-V interval) is one-fifth of a second. Digitalis may cause, through interference with this conduction, (1) a prolongation of the A-V interval, or (2) in toxic doses may lead to incipient, or even less frequently to complete heart-block. These effects, the first of which can only be ascertained by tracings, are toxic, and call for the stoppage of the drug. On the other hand this prolongation of the auriculo-ventricular interval makes it useful in the treatment of auricular fibrillation, so that digitalis blocks many of the auricular impulses to pass into the ventricle.

4. In therapeutic doses it is doubtful if digitalis has any constricting effect on the coronary arteries. The increased aortic pressure, the prolonged diastole, and greater contraction in systole resulting from therapeutic doses of digitalis, lead to a vastly improved coronary circulation, with the result that the nourishment of the heart-muscle is improved. In toxic doses, however, *coronary constriction* does occur, and this may cause such muscular weakness that the condition known as *pulsus alternans* may arise.

5. Small doses of digitalis have no direct action on the blood vessels, but toxic doses cause constriction of the arteries, partly by action through the vaso-constrictor centre and partly by direct action on the muscle walls. The heart muscle being more sensitive to digitalis than the arterial walls, the amount of digitalis which produces a definite effect on the vessel is fatal to the heart, and the consensus of opinion among modern workers on the circulation is that *in therapeutic doses digitalis does not cause any arterial constriction and does not raise the general blood-pressure*.

Temperature.—In medicinal doses it has no influence on the temperature, but in toxic doses it reduces it even in health. The effect is possibly due to increased activity of the heat controlling centre (Cushny).

Nervous system.—In medicinal doses it has no influence on the brain, the cord, and the sensory and motor nerves. In large doses it causes giddiness, headache, dimness of sight and disturbed hearing. Flashes of light, and a blue halo around bright objects also appear before the eyes. All these symptoms are probably due to some disturbance in the cerebral circulation. The reflex excitability and motor nerves are depressed only by toxic doses.

Digitalis stimulates some of the medullary centres. In toxic doses, or when continued long, it causes vomiting by stimulating the vomiting centre; it stimulates the vagal centre causing slowing of the rate of the heart; and stimu-

lates the vaso-motor centre causing a rise of blood pressure (not observed in therapeutic doses).

Kidney.—Digitalis is a powerful diuretic in cardiac dropsies, and the effect is proportional to the improvement in circulation. In dropsies not due to circulatory failure, it has little or no effect. Since it produces no diuresis in healthy individuals the diuresis cannot be due to any action on the kidneys. According to Sollmann the following factors improve renal circulation, *viz* —(a) relief of venous pressure; (b) increased output of the heart; and (c) the hydræmia resulting from the absorption. If large doses are administered, the vaso-constriction may be so great as to stop the excretion altogether. It takes about 48 hours to produce any diuretic effect after commencing the treatment with digitalis.

It has no action on the composition of the urine.

Onset and duration of action—Given by the mouth in small therapeutic doses the effects appear very slowly, and it takes about 24 to 36 hours for the circulatory action and 72 hours for the diuresis. But the appearance of digitalis effect depends largely upon the dose. Thus when full doses are given the effects appear within 2 to 4 hours. Digitoxin has the property of fixing itself to the heart muscle and once the fixation has taken place its removal is very difficult, in fact it cannot be removed by any chemical or physiological measure (Cloetta). Both digitoxin and digoxin get fixed more firmly than other cardiac glycosides, e.g. strophanthin. This peculiarity of its action makes the drug so valuable therapeutically. Its products are eliminated from the cardiac muscle very slowly. It is for this reason that symptoms of poisoning may occur even though the dose may not be increased, provided the drug is continued for a prolonged period. Indeed therapeutic effects appear when an adequate concentration of the drug is produced in the blood and once established the effects continue for some time even after the stoppage of the drug.

Cumulative action.—Digitalis is not given in sufficient doses for fear of cumulative action, for when given for a long time it sometimes shows symptoms of poisoning even when its dose has not been increased. This is known as the cumulative effect of the drug, and is due to the retardation of its excretion or destruction. The danger of cumulative action has been exaggerated, for the symptoms disappear in a few hours as soon as the use of the drug is discontinued. The active principles, not being eliminated as fast as they are absorbed, accumulate in the system. The symptoms of excessive action are:—

1. Nausea and vomiting from stimulation of the vomiting centre. These are the first signs of toxicity and full therapeutic effect.

2. A marked decrease in urinary secretion due to constriction of the renal vessels.

3. Headache

4. A progressive slowing of the pulse rate from excessive vagus stimulation, which should never be allowed to go below 60

5. The development of sinus arrhythmia, premature contractions, dropped beats (incipient heart-block) from depression of A-V bundle, extra-systole, tachycardia and fibrillation from hyperexcitability of the cardiac muscle. In fact any form of cardiac irregularity may follow digitalis administration, and it becomes rather difficult to differentiate whether the irregularity is the result of digitalis administration or a part of the clinical picture.

When any of the above symptoms arise the administration of the drug should be at once stopped.

Elimination.—It is chiefly excreted by the kidneys and partly by the gastro-intestinal mucous membrane. But its elimination is very slow, often slower than its absorption, and its long continued use may cause cumulative effects.

THERAPEUTICS

Valvular diseases of the heart.—Digitalis is a valuable drug in diseases of the heart. It is of supreme value in those conditions of the heart which have departed most widely from the normal. If the muscles are healthy, but otherwise over-worked, exhausted and fatigued, digitalis by its effect on the cardiac muscle will restore its tone. In valvular diseases of the heart where the incomplete emptying has caused the ventricles to dilate and there is an over-increasing strain on the muscle, digitalis has a wonderful influence in restoring the dilated and weakened ventricle to a state of efficiency. Under its use a quick, weak and irregular contraction becomes slower, stronger and regular. As the diastolic period is prolonged, the heart gets more time for nutritive repair, and for more efficient subsequent contraction, from the flowing in of more blood from the dilated auricle. Since digitalis acts by its powerful effects on the cardiac muscle, it is of greater value in ventricular dilatation which follows mitral and tricuspid regurgitation than in auricular dilatation. Digitalis therefore relieves dyspnoea, cough, venous engorgement of the lungs and of the abdominal organs, oedema, dropsy, and many other symptoms due to mitral regurgitation. It also benefits mitral constriction, as by lengthening the period of diastole it allows the normal amount of blood to pass through the constricted orifice

In the first stage of aortic regurgitation digitalis is considered useless or positively harmful as it prolongs the

diastolic interval and thus allows more time for the blood to flow back from the aorta. In most cases, however, the period of diastole is not prolonged, and clinical evidence shows that in some cases of aortic valve failure digitalis is of undoubted value. In the second stage, when the ventricle dilates, and the auriculo-ventricular orifice enlarges, producing secondary mitral regurgitation, digitalis is of great value. But it must be given with great caution, for sudden syncope may occur if the patient does not keep to his bed. Cases of pure obstruction do not require any drug, as compensatory hypertrophy may gradually take place without them. But when we wish to increase the contractile force of the heart in order to drive more blood through the obstructed aorta, or when from such an obstruction mitral disease has set in, digitalis in small doses does immense good.

Another great field of usefulness of digitalis is in **cardiac irregularities**. It is of great value in **auricular fibrillation** which occurs in advanced myocardial and valvular lesions. In this condition the over-stretched auricular muscles are unable to make concerted contraction and the impulses arise in abnormal parts of the auricle, and the auricle is kept in continual inco-ordinate activity. These numberless irregular impulses pass into the ventricle and the ventricle responds without any regularity in rhythm or strength. The action of digitalis in this condition is striking. By blocking the auricular impulses the ventricle responds less frequently and the number of beats becomes less and the heart beats regularly and more efficiently with the result that the general circulation improves. Fifteen to thirty minims, three or four times a day, should be given at first, and if the fibrillation is permanent, it should be followed by smaller doses once or twice a week, or once a day for some time. It acts by impairing the conductivity of the auriculo-ventricular bundle, *i.e.* by establishing partial heart-block, whereby many of the superfluous auricular impulses are blocked and do not pass to the ventricles.

Digitalis is also of great value in **auricular flutter**. In this condition the auricle is also the seat of abnormal excitation and beats at a very rapid rate though regularly. Given in full doses, digitalis will change the flutter into fibrillation and by reducing the conductivity of the bundle of His will make the ventricles beat slowly.

Digitalis is contra-indicated in **partial heart-block** as it tends to increase the degree of block. But opinions differ in complete heart-block, indeed some authorities recommend it on the ground that by slowing the rate of the auricle and increasing that of the ventricle it will help to bring the auricular and ventricular rates more nearly together. It is to be avoided in *bundle-branch block* and in *sino-auricular block*.

Fatty heart.—Digitalis should not be given in fatty degeneration of the heart, as the increased force of systole may lead to rupture of the degenerated muscle fibres.

Other cardiac diseases.—In many primary diseases of the muscular structure, such as acute or chronic myocarditis, with or without vegetative growths, pericarditis, endocarditis with or without valvular lesions, digitalis helps to quiet and regulate the action of the heart. Many functional diseases of the heart, such as palpitation, irregular cardiac beat due to dyspepsia, are benefited by digitalis, but it must be used with caution as it may bring on indigestion. In many irritable conditions of the heart, especially in persons who take excessively hard exercise, such as rowing or long marches with heavy knapsacks, or in persons of a neurotic temperament, digitalis is considered highly beneficial. The dilatation of the right side of the heart which so often accompanies chronic diseases of the lungs is also relieved by digitalis.

Digitalis as a diuretic.—Digitalis is the most reliable and often successful diuretic in cardiac oedema, and the majority of cases require no further medication. Remarkable results follow rapid digitalization, although the changes in the rate of the heart and occurrence of diuresis may not necessarily run together. Since digitalis causes constriction of vessels, including those of the kidneys, in large doses, massive doses do not necessarily act more efficiently though the effects are often more dramatic. It also acts as a diuretic in nutritional and anæmic oedema as where the circulation is impaired. It is however of not much use as a diuretic in dropsies from other causes, *e.g.* in Bright's disease, where the drugs of the purine group are generally preferred. But in chronic Bright's disease when the anuria is the result of deficient circulation, digitalis, especially the Guy's pill, is of great service. Since therapeutic doses do not materially alter the blood-pressure, high arterial pressure *per se* is no contra-indication to the use of digitalis.

Acute febrile diseases.—Digitalis is often used in different febrile diseases where the heart becomes affected from the toxins of the infection or from high temperature. In these conditions digitalis may be used to improve the tone of the heart and produce slowing of its rate. Its use has also been advocated in pneumonia, but the different factors such as high temperature, toxins, or the invasion of the heart with specific organisms exert an influence over the heart which digitalis cannot overcome. It has therefore been suggested that it should be used from the very commencement on the idea that if digitalization of the heart is done early it will prevent the toxin from affecting the heart. It is however debatable whether early digitalization will reduce the case mortality in pneumonia.

Exophthalmic goitre.—Whether given alone or with iron and quinine, digitalis is considered to be a valuable remedy in this disease. but very often it is found to produce little effect.

Caution.—It should be remembered while treating cardiac disturbances, that the effect of digitalis varies in different classes of cases. that while it is of great value in certain diseases of the heart, its effects are not so marked in others, and in a third class of cases its use is contra-indicated—being harmful or dangerous. Great care and caution should therefore be observed in the selection of cases for the exhibition of digitalis. The best way to avoid any untoward effect during a course of digitalis treatment is to suspend the administration of the drug for a few days as soon as the physiological reaction is reached, as evidenced by slow pulse, nausea, vomiting, and diarrhœa. In this way the cumulative action is avoided. Cases of sudden deaths are on record when the drug has been pushed without stoppage after it had affected the heart.

It is contra-indicated in partial heart-block, cerebral hæmorrhage, embolism of recent origin and aortic aneurism in its later stages; and should be used with caution in pronounced arterio-sclerosis.

Prescribing hints.—The effect of digitalis in cardiac disorders is shown by slowness of the rate of the heart and diuresis, and these are produced in therapeutic doses before any toxic effects—nausea, vomiting, coupled beats—are observed. Digitalis is best prescribed in the form of tincture, which should be given alone in 15-30 ms. doses three times a day to be diluted with water before taking, because the tincture does not maintain its strength long when kept diluted in water. This dose should be pushed till a definite response is observed in either the pulse, the urine, or the nausea, when its use should be stopped and the heart-rate carefully watched. When the heart-rate shows signs of increase, half the dose should be given and the dose regulated as occasion arises aiming to maintain compensation and keeping the pulse to about 80, with the smallest possible dose. It should be noted that practically no therapeutic effect is produced until the total dosage nearly approaches the toxic and as a rule no beneficial effects are observed till the second or third day. It has therefore been suggested that in urgent cases, a single large dose followed by smaller doses. until some definite response is obtained, should be preferred. Since about 20 ms. of the tincture is daily destroyed and excreted in twenty-four hours, it is only necessary to give this amount daily as a maintenance dose after the patient has been digitalized.

The other method of giving digitalis is that of Eggleston. He gives 7·5 c.c. of the standardised tincture per 100 pounds

of body weight as the first dose; followed in six hours by one-fourth of the total dose, then smaller fractions every four or six hours till full response is reached. With this method the effects appear within 2 to 5 hours after the first dose, reaching its maximum within 24 hours. This effect may continue for 14 to 15 days without further administration. Much care and caution is necessary when using digitalis in such large doses and unless one is certain that the preparation is properly standardised such large doses should not be used. Moreover one should ascertain whether the patient had digitalis treatment within a fortnight before giving such large doses.

Irritation of the stomach is a great drawback to digitalis administration, when parenteral administration becomes necessary. Digoxin being water-soluble may be used intravenously like strophanthin, and will often produce quick effect; but great care is necessary in giving digoxin intravenously, and the standard method of administration should be by the mouth. Given by the mouth the effects are observed within an hour and is very useful in auricular fibrillation. Given intravenously the effects are observed within 5 to 10 minutes reaching its maximum in one to two hours.

Although digitoxin and digitalin are insoluble in water, the infusion contains some of them in colloidal solution brought about by digitonin, which, though not absorbed from the intestine, helps the solution of other glycosides. Since these glycosides undergo decomposition and form resin-like bodies when kept in solution for long, old preparations, specially the infusion, are useless therapeutically and may be harmful.

Diuresis generally follows the administration of digitalis in cases of heart failure, and if there is no diuresis, the use of the drug will not produce any beneficial results. In fact the secretion of urine is not increased unless there is œdema present, although digitalis may be given even in massive doses.

Since therapeutic doses do not raise the blood-pressure, high blood-pressure is not a contra-indication to the use of digitalis, although the pulse pressure may be increased as a result of the fall in the diastolic level in cases of heart failure.

Though incompatible with iron on account of the tannin it contains, digitalis is often advantageously given with iron; but the resulting inky mixture should be cleared by the addition of diluted phosphoric acid.

ST P ANT US

Strophanthus. (*Strophanth.*)

Syn.—*Strophanthus* seeds.

Source.—The dried ripe seeds of *Strophanthus kombe* free from the awns.

Characters.—Lanceolate to linear-lanceolate, acuminate, about 12 to 18 mm. long, 3 to 5 mm. broad, blunt base, tapering apex, sides flattened, one side having a median ridge and the other being convex covered with silky appressed hairs. Characteristic odour. Taste, very bitter.

Composition—It contains from 7 to 10 p.c. of a mixture of glycosides, *K-Strophanthin*, together with about 25 p.c. of fixed oil. *K-strophanthin* consists of *cymarín*, *k-strophanthin-β* and other glycosides, and yields on hydrolysis aglucone strophanthidin, cymarose, and a sugar. *Choline*, oil and resin.

OFFICIAL PREPARATION

1. **Tinctura Strophanthi.**—It is equivalent in activity to a 0.42 p.c. solution of the International standard Ouabain B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil.

STROPHANTHIN

Strophanthin. (*Strophanthin.*)

Syn.—Kombe *Strophanthin*.

Source.—A mixture of glycosides obtained from *Strophanthus*.

Characters.—A white, or yellowish white powder, minute crystals being visible under microscope. Moderately *soluble* in water, and in alcohol (90 p.c.), less so in dehydrated alcohol. Solution in water or alcohol is neutral to litmus, and is dextrorotatory.

B.P. Dose.— $\frac{1}{10}$ to $\frac{1}{6}$ gr. or 0.00025 to 0.001 gram. by intramuscular or intravenous injection.

PHARMACOLOGY

Locally.—*Strophanthin* is an irritant to the mucous membrane, but less powerful than *digitalis* glycosides. On the other hand it has an anæsthetic action on the conjunctiva and cornea, and was used as such before the introduction of cocaine.

Internally.—Although *strophanthus* is absorbed more rapidly than *digitalis* and does not produce any local irritation to the same extent as *digitalis*, it is easily destroyed by the digestive juices, and loses much of its effects when given by the mouth.

Heart and circulation—Action exactly *similar to that of digitalis*. Its action is very rapid, producing its effect within half to one hour. But it is more dangerous since it induces more readily the condition known as “*delirium cordis*,” and its absorption and elimination are very uncertain. It has no effect on the peripheral vessels and therefore does not cause vaso-constriction like *digitalis*.

Kidneys.—It is a diuretic in a normal person, and as it raises the blood-pressure without constricting the peripheral renal vessels it sends more blood through the kidney and acts as a more efficient diuretic than *digitalis*. Like other glycosides it is partly destroyed in the body and is readily excreted from the heart muscle and therefore its action is short and is not cumulative.

THERAPEUTICS

Strophanthus is probably the most useful drug in the treatment of cardiac decompensation. Its only disadvantage is that when given by the mouth the glycoside is decomposed in the alimentary canal and its effects are uncertain. Strophanthin being soluble in water and more uniform in composition is largely used intravenously and often in combination with glucose. It is valuable in severe acute decompensation specially when associated with cardiac asthma

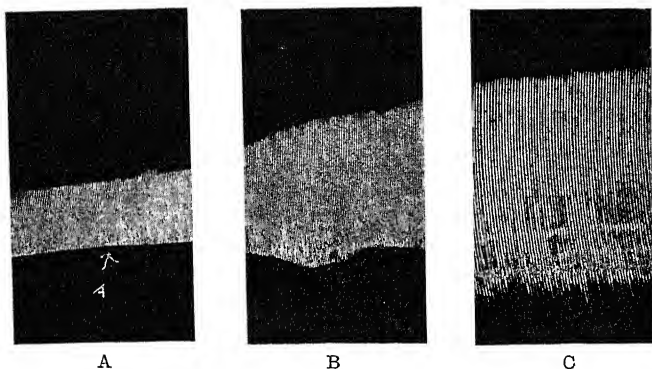


FIG. 8.—Effect of Strophanthin on Isolated Rabbit's Heart Perfused with Locke's Solution.

At A strophanthin 0.2 mg. was given; note the heart acts more powerfully, the contractions become stronger. Figure B shows the effect after 15 minutes and the figure C, 30 minutes after B.

and pulmonary œdema; in acute heart failure following infectious disease, after paroxysmal tachycardia or extreme degrees of flutter-arrhythmia; when digitalis causes nausea or vomiting; as an alternative to digitalis in many cases of complete auriculo-ventricular block with bradycardial ventricular autonomy; and when insufficiency appears to affect the left more than the right side of the heart. This method however is not suitable where a prolonged treatment is necessary, when digitalis will be found more convenient. With digitalis the effect of gradual absorption is more beneficial to the heart than the daily use of the intravenous injection. It has been used by intramuscular injection combined with novocaine (0.5 mg. in a muscle being as effective as 0.25 mg. in a vein).*

The advantages of strophanthin over digitalis are :—(a) Effect is quicker, being produced in a few minutes; digitalis given by the mouth takes several hours, often two to three days to produce the full effect; (b) a prolonged improvement of systolic activity, without prolonging the diastole

**British Medical Journal, Epitome*, Dec. 19, 1936.

which digitalis often causes; and (c) the absence of cumulative effect.

SCILLA

Squill. (Scill). N.O. *Liliaceæ*

Source.—The bulb of *Urginea Scilla*, divested of its dry membranous outer scales, cut into slices, and dried.

Characters.—In curved, very pale yellow, somewhat translucent strips, tapering towards both ends, from 0.5 to 5 cm. long; pulverisable when dry, not when moist. Inodorous, bitter.

Composition.—A crystalline glycoside *Scillaren A*, $C_{36}H_{52}O_{13}$, and an amorphous soluble glycoside *Scillaren B*. The former on hydrolysis yields the aglucone scillaridin and rhamnose.

OFFICIAL PREPARATIONS

1. *Acetum Scillæ*.—10 p.c. B.P. Dose.—10 to 30 ms or 0.6 to 2 mils.
2. *Oxymel Scillæ*.—Active constituents equivalent to 5 p.c. w/v of squill. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
3. *Syrupus Scillæ*.—Equivalent to 4.5 p.c. w/v of squill. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
4. *Tinctura Scillæ*.—Equivalent to 10 p.c. w/v of squill. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.

PHARMACOLOGY

Internally—Squill acts like digitalis in many respects. The description of the latter will therefore apply to that of the former with the following distinguishing characteristics :—

1. Its action on the heart is almost the same as digitalis and when given intravenously causes a greater rise of blood pressure; but administered by the mouth its absorption is slow and less complete and therefore its effect on the heart is not so marked.
2. It is a *more powerful gastro-intestinal irritant than digitalis*, causing nausea, vomiting, purging (even bloody stools), and intense inflammation of the mucous membrane in full doses, and occasionally in medicinal doses. In many cases this irritant effect is not observed.
3. It is an *expectorant* acting reflexly through gastric irritation.
4. It is a *more powerful diuretic* than digitalis. It acts in two ways :—(a) like digitalis by improving the circulation, and (b) the active ingredients being excreted by the kidneys act as direct stimulants to the renal cells, and may cause considerable irritation of these organs.

THERAPEUTICS

Internally.—Squill can be given in cardiac and other forms of dropsy. But its irritant properties are somewhat mitigated when it is combined with digitalis. Even then it

is safe to occasionally suspend its administration for a while. Guy's pill (page 267) is an excellent combination, and an efficient diuretic in cardiac dropsy.

It is rarely prescribed alone and is contra-indicated in acute renal disease or if there be gastro-intestinal irritation.

It is largely used as an expectorant, but should not be given in acute bronchitis. It is of great value in old-standing pulmonary diseases, where, besides acting as an expectorant, it tones up the heart the right side of which is so frequently dilated. In the chronic bronchial affections of children, the oxymel or syrup is always serviceable in 10 to 15 ms. doses, but its indiscriminate use in all varieties of bronchial affections is to be deprecated. Squill becomes doubly beneficial in chronic catarrh of dropsical patients.

APOCYNUM (*Not official*) *Syn*—Canadian Hemp—Root of *Apocynum cannabinum*

Composition—It contains the glycoside *cymarin*, to which its action is due

Dose—1 to 5 g's. or 0.06 to 0.3 grm. of powdered root

NON-OFFICIAL PREPARATION

1 Tinctura Apocyni, B.P.C.—1 in 10. **Dose**—5 to 10 ms. or 0.3 to 0.6 mil.

PHARMACOLOGY AND THERAPEUTICS

Apocynum is a gastro-intestinal irritant in large doses, giving rise to nausea, vomiting and purging.

It possesses all the properties of digitalis on the circulation but the effects on the vaso-constrictor are relatively strong and it is not cumulative. It directly stimulates the unstriped muscles. It is a powerful diuretic and is largely used in cardiac dropsies. It is also recommended in dropsies due to cirrhosis of the liver and is also useful in causing the absorption of pleuritic effusion. For these reasons it is commonly known in America as the "Vegetable Trocar." Cymarin in doses of 0.1 to 0.5 mg. has been used intramuscularly or intravenously like strophanthin.

2. Cardiac Depressants

Excepting the central nervous system the heart is more liable to be affected by poisonous drugs than any other tissues of the body. When the heart is depressed, the force of contraction becomes less strong, the conduction is diminished, and the rate is reduced. The reduction of the rate of the heart without depressing the force of the contraction is often desirable in disease. Quite a large number of drugs act as cardiac depressants. All hypnotics and general anæsthetics also act as cardiac depressants, and those containing chlorine molecule are more so.

AC NITU

Aconite. (Aconit.)

Syn.—Monk's Hood. **Syn. I.V.**—*Katbis*, *Dudhrabish*, Hind.

Source—Dried root of *Aconitum Napellus*.

Characters.—Dark brown, obconical; usually 4 to 10 cm. long, from 1 to 3 cm. wide at the crown, to which is attached the base of

stem or a bud and showing root scars. Internally, starchy, showing a stellate cambium. Odour, slight; taste, slight, followed by a persistent tingling and by numbness.

Composition.—(1) *Aconitine* (acetylbenzoyl-aconine), the chief active principle. (2) *Picroaconitine* (Benzoyl-aconine). (3) *Aconine*. (4) *Aconitic acid* and starch.

OFFICIAL PREPARATION

1. *Linimentum Aconiti*.

NON-OFFICIAL PREPARATIONS

1. *Chloroformum Aconiti*, B.P.C.—Root 100, Dilute Ammonia Solution 25, Absolute Alcohol and Chloroform, each *g s* to 100.

2. *Tinctura Aconiti*, B.P.C.—1 in 6 Contains 0.04 p.c. ether-soluble alkaloids. *Dose*—2 to 5 *ms* or 0.12 to 0.3 *ml*

3. *Linimentum Aconiti Oleosum*, B.P.C. *Syn.*—*A.B.C. Liniment*.—Aconite, Belladonna and Chloroform liniment, equal parts

PHARMACOLOGY

Externally.—When applied to the skin rubbed up with chloroform or some fatty substance, without which it is not absorbed, aconite first stimulates then paralyses the terminations of the sensory nerves, thereby causing tingling, numbness and anæsthesia. It is rapidly absorbed from all mucous surfaces.

Internally. **Gastro-intestinal tract**—The same tingling, numbness and anæsthesia are produced when aconite is applied to the tongue, followed by salivation caused reflexly through irritation of the nerve-endings of the tongue and nausea. In large doses it causes gastro-intestinal irritation such as nausea, vomiting and diarrhoea.

Heart and circulation.—In small doses it makes the heart slow, diastole is prolonged and the systole is weakened. The pulse becomes weak and soft and, if the dose is not increased, does not become irregular. The slowing is due to stimulation of the vagal centre and does not occur if the vagus is cut. According to Cushny aconite has no influence in slowing the rate of the heart in ordinary doses, in fact there is some quickening when maximum therapeutic doses are used through the nausea induced by the irritant effect in the stomach. In large doses it has a direct effect on the heart muscle and the heart becomes feeble, irregular and accelerated, auricular-ventricular arrhythmia being set up, and finally the ventricle passes into fibrillation and the heart stops in diastole. These effects of aconite cannot be elicited in man in therapeutic doses and are due to the direct action on the cardiac muscle. The blood-pressure falls chiefly from lessened output from cardiac depression in the early stage, while later the vaso-motor centre is also paralysed.

Respiration.—In small doses it stimulates the respiratory centre, and breathing becomes deep and frequent, but it

is soon followed by depression when the respiration becomes slow, deep, irregular and laboured. It is possible that some of the effects are reflex through vagus effects in the lungs. Death takes place from **asphyxia** due to respiratory failure from paralysis of the centre

Temperature.—A febrile temperature is lowered by aconite; the mechanism of this effect is not well understood, but increased diaphoresis is one of the factors.

Nervous system.—Whether applied locally or taken internally, aconite first stimulates and then depresses the periphery of the sensory nerves. The ends of the motor nerves are also somewhat stimulated and then depressed, and the nerves conveying thermic sensations are affected in poisoning. It first stimulates but soon depresses, the vagal, vaso-constrictor and respiratory centres. The brain remains unaffected. The pupils first contract, then dilate. Large doses first stimulate and then depress the motor centres in the spinal cord. The convulsions observed in poisoning are due to asphyxia.

Skin—Perspiration is increased possibly due to dilatation of the vessels of the skin. It sometimes gives rise to an erythematous rash

Elimination—It is mostly excreted in the urine, although traces of the active principle have also been detected in saliva, stomach, bile and sweat.

Acute toxic action.—Within a few minutes after swallowing a poisonous dose of aconite, severe tingling and burning followed by numbness are noticed in the mouth and gullet. Intense abdominal burning; excessive salivation; vomiting and diarrhoea; cold, clammy skin and profuse sweating; tingling, formication, and numbness of the skin; small, feeble, irregular pulse; fixed, staring eyes; pupils first contracted and then dilated; difficult respiration; muscular weakness; prostration; fainting; sometimes convulsions; lastly death either from asphyxia or occasionally from syncope. Consciousness remains more or less clear till death.

Treatment.—Emetics, pump, stimulants, hot bottles, friction, sinapisms to the heart. Tinct digitalis 20 to 30 ms., strychnine up to $\frac{1}{8}$ gr. and atropine $\frac{1}{64}$ gr. may be used. Adrenaline or strophanthin intravenously. Artificial respiration often saves life.

Physiological antagonists.—Digitalis, strychnine, atropine, ammonia, ether and alcohol.

Benzaconine.—It is bitter and less toxic and does not cause tingling. It slows the heart-beat, the ventricles contracting once for every two or three auricular contractions. It interferes with the motor nerves and does not paralyse the sensory nerves.

Aconine, though bitter, does not cause numbness or salivation. It strengthens the ventricular systole and opposes inco-ordination of the heart-beat caused by aconitine. In large doses it depresses respiration and paralyses motor nerve-endings like curara.

THERAPEUTICS

Externally.—Aconite in the form of a liniment is applied for the relief of pain in neuralgia, sciatica, muscular rheumatism and inflammatory joint affections. The addition of

chloroform increases the efficacy, as it facilitates absorption. For this reason, *Chloroformum Aconiti*, B.P.C. or the A.B.C. liniment are more effective than the B.P. preparation.

Internally.—Aconite is not so largely used now in fevers as formerly. Careful observations by Mackenzie and Price failed to elicit any slowing of the rate of the heart with aconite and it is rarely used in the treatment of fevers. Nowadays its use is confined chiefly to **inflammatory fevers**, such as pleurisy, peritonitis, tonsillitis, sore throat, etc. It should be given in small doses (1 or 2 ms. of the tincture) rather frequently until there is a fall of temperature, sweating and relief of the symptoms. It should never be given in continued fevers, such as typhoid.

CLASS B: Drugs acting on the Vessels

The arteries are elastic *nervo-muscular* tubes, whose calibre constantly changes owing to a variety of influences, which are transmitted by the vaso-constrictor and vaso-dilator nerves, from the vaso-motor centre located in the medulla, and certain subsidiary vaso-motor centres in the spinal cord. The arterial muscles are kept in a constant state of contraction or tone, which enables them to counteract the pressure of the fluid within. This tone is chiefly due to continuous reception of subminimal impulses from the vaso-constrictor centre. The vaso-dilators differ from the constrictors in that they are not in tonic activity, and that they produce dilatation by inhibiting the contractile impulses, the arteries having no dilator muscles. Both the constrictors and dilators belong to the autonomic system, and when both sets are stimulated the constrictor effect predominates, but if the stimulation is prolonged, the constrictors are the first to show signs of exhaustion, so that eventually there is dilatation.

The vaso-motor system may be influenced by drugs acting upon any part from the centre to the nerve-endings, and also reflexly by afferent impulses coming to the centre from other parts of the body. It should be noted however that some of the arteries—the coronary, pulmonary and cerebral—have no vaso-constrictor nerves. But the maintenance of efficient coronary circulation is most essential, as on this depends the activity of the heart.

By the *blood-pressure* is meant the pressure to which the walls of the arteries are subjected. The rise and fall of the blood-pressure depend upon the activity of the vaso-constrictor and vaso-dilator nerves respectively. Besides the afferent influences affecting the pressure there are other circumstances which greatly modify it. They are (1) the heart's output in a given time; (2) the total quantity of blood in the circulation; (3) the peripheral resistance; and (4) the viscosity of the blood.

The pressure may be raised by (1) general constriction of the arterioles; (2) increase in heart's output; (3) increased volume of blood; and (4) slightly by increased viscosity of the blood. The pressure is lowered by the opposite conditions.

The arterioles, specially those of the splanchnic area, are the most important regulators of the arterial pressure so that when these arterioles dilate so much blood passes into them that no blood is left for the brain and other vital organs, thus causing faintness and even death. Even when the arterioles remain contracted the pressure cannot be maintained if the heart fails, or if there is much loss of blood.

Capillaries.—Since the normal exchanges between the blood and the tissues take place through the capillary walls, maintenance of efficient capillary flow is an important function of the circulatory organs. The arterioles being actively contractile act as flood-gates and regulate the amount of blood passing through any given set of capillaries. The capillaries themselves are capable of contraction and dilatation and are controlled by chemical and nervous stimuli, and though controlled by sympathetic are not affected by adrenaline beyond a certain distance from the arterioles. Pituitary is supposed to contain a hormone which maintains the normal tone of the capillaries. Histamine, arsenic and antimony dilate the capillaries. Dilatation of the capillaries of the splanchnic area is also the cause of fall of blood-pressure in surgical shock.

Carotid Sinus.—This is the name given to the specially innervated part of the vessels and tissues in the neighbourhood of the bifurcation of the common carotid into its branches and the carotid body, which is related to the carotid sinus. Recent studies by different observers have elucidated its importance in the regulation of circulation and respiration. It has been pointed out by Heymans that the regulation of blood-pressure through adrenaline secretion is controlled reflexly by the sinus nerves which normally exert a tonic inhibitory influence on the vaso-motor centre. He has further shown that neither the adrenal glands nor the centres controlling them are acted on directly by the level of the blood-pressure. Stimulation of the sinus electrically or by stretching its walls by pressure from within provokes a combined reflex of cardiac inhibition and fall of blood pressure just in the same way that follows the stimulation of the central end of the vagus. A rise of pressure in the sinus inhibits and a fall of pressure in the sinus stimulates adrenaline secretion. During rest the sinus nerves exert a tonic inhibitory influence over adrenal activity.

A. Drugs which raise the blood-pressure

1. *Acting by stimulating the vaso-motor centre*—All drugs which stimulate the central nervous system also stimulate the vaso-motor centre in the medulla. They cause a rise of blood-pressure by constricting the vessels of the splanchnic area. It is possible that these drugs increase the output of adrenaline. The drugs belonging to this group are strychnine, caffeine, digitalis, camphor, atropine, cocaine, etc. Alcohol given in concentrated solution stimulates the vaso-motor centre reflexly and causes a rise of blood-pressure. After absorption the peripheral vessels dilate and there is a fall of pressure. Excess of CO₂ in the blood, as happens in asphyxia, also stimulates the centre. The centre may be reflexly stimulated by counter-irritants, which cause stimulation of the sensory nerves and vaso-constriction.

2. *Acting on the vaso-motor nerve-endings.*—The normal tone of the vessels depends upon the activity of the adrenal glands, and removal or disease of these glands is followed by fall of pressure. Adrenaline, ephedrine and ergotoxine (in small doses) cause powerful vaso-constriction and a rise of pressure by acting on the sympathetic nerve-endings. Ergotoxine however causes subsequent depression and paralysis of the augmentor nerve-endings of the sympathetic and causes a fall of pressure.

3. *Acting on the muscles.*—These when administered either by the mouth, or as injection, cause vaso-constriction by acting on the muscles of the vessels. They are digitalis, posterior pituitary extract, barium and veratrine. Digitalis however causes vaso-constriction in doses toxic to the heart, and its therapeutic administration is not followed by any such action.

4. *By increasing the volume of blood.*—During collapse and shock specially from hæmorrhage the pressure diminishes which can be

raised by (a) *transfusion of blood*; and (b) *injection of normal saline*. But since saline infusion has a tendency to diffuse into the tissues, the excess of fluid is readily excreted by the kidneys. A more permanent increase of blood volume is obtained by adding some colloid in the transfused fluid, as injection of gum saline (see page 85).

B. Drugs or measures which lower the blood-pressure

1. *Acting by depressing the vaso-motor centre*.—Alcohol, chloral hydrate, ether, chloroform and narcotics depress the vaso-motor centre and cause a fall of pressure. They cause the vessels of the skin to dilate with consequent loss of heat. Coal tar antipyretics also produce the same effect. Surgical shock which occurs immediately after an injury is followed by a fall of blood-pressure which has been attributed to exhaustion of the vaso-motor centre which does not respond to normal afferent stimulation.

2. *Acting on the arterial muscle*.—These drugs when used subcutaneously, or taken by the mouth, or some of them when inhaled, dilate arterioles and cause a fall of pressure. Certain products of metabolism also cause vaso-dilatation, as happens with slight increase of acidity of blood. Drugs belonging to this group are amyl nitrite and nitrites, organic nitrates, acetyl-choline, theobromine.

3. *Acting by diminishing the volume of blood*.—This may be done by bleeding, venesection or by application of leeches. The volume of circulating blood may be reduced by diminishing the plasma. Purgatives and diaphoretics by withdrawal of fluids from the body reduce plasma volume.

4. *Acting by causing capillary paralysis*.—Histamine has a special toxic effect on the capillaries which are dilated causing a fall of pressure although the arterioles are constricted. By producing abnormal permeability of the capillaries it helps plasma to pass from blood to the tissues. Arsenic and antimony in poisonous doses possess a specific action on the capillaries and cause dilatation of the capillaries of the mucosa of the alimentary canal. Secondary shock also causes a fall of blood-pressure and is supposed to be due to the production by the tissues of some substance having action similar to histamine.

C. Drugs or measures acting locally on the vessels

1. *Local vascular stimulants*, or remedies which dilate arterioles when locally applied to the skin. They are alcohol, iodine, ammonia, tartar emetic, arsenious acid, camphor, cantharidin, capsicum, phenol, creosote, croton oil, chloroform, ether, mustard, volatile oils, hot applications, etc.

2. *Local astringents, hæmostatics or styptics* are drugs which constrict the vessels when locally applied. They also cause shrinkage of the mucous surface. Those acting by contracting the muscular fibres are adrenaline, cold from any means, as evaporation of ether, ethyl chloride, or by application of ice. Vegetable astringents, alum, silver, lead, iron, etc., act by coagulating the proteins in the tissues surrounding the vessels; they have no action on the muscular coat of the vessel walls. Snake venom (Russell's viper) coagulates the blood and stops bleeding when locally applied.

Since local astringents are precipitated by proteins they cannot be absorbed nor can they exist in the blood and tissues in an effective form. It therefore stands to reason that these drugs cannot have any remote action and cannot stop bleeding when used internally except from the part where it directly comes in contact.

Remote hæmostatics are drugs which when given internally by the mouth or by injection stop internal hæmorrhage by helping coagulation of the blood. These are used mostly in hæmophilia, hæmoptysis and other forms of internal hæmorrhages. They are calcium, congo red, hæmostatic serum, etc.

Some drugs when used internally constrict the vessels after

absorption. They are chiefly adrenaline, posterior pituitary, digitalis, ergot, strychnine, CO₂, etc. These are rarely used for the purpose of stopping hæmorrhage, except ergot and pituitary extract in cases of uterine hæmorrhage.

Vaso-constrictors are drugs which cause constriction of vessels either when administered by the mouth or when used locally.

1. Drugs Raising the Blood-pressure

Vaso-constrictors

A RENALINA

Adrenaline. (Adrenal.)

Syn.—Epinephrine; Suprarenin; Adnephrine.

Source.—It is *l-a-3*: 4-dihydroxyphenyl- β -methylamino-ethanol. An active principle of the suprarenal gland. Obtained from an acid extract of the glands of certain mammals, or by synthesis.

Characters.—A colourless or pale buff-coloured, sphæro-crystalline powder. Sparingly soluble in water; *insoluble* in alcohol (90 p.c.), and in ether. *Soluble* in aqueous solutions of mineral acids, and of sodium and potassium hydroxides. Not stable in neutral or alkaline solution, which becomes red on exposure to air. Natural adrenaline is laevorotatory.

B.P. Dose.— $\frac{1}{800}$ to $\frac{1}{100}$ gr. or 0.0001 to 0.0005 grm.

OFFICIAL PREPARATION

1. *Liquor Adrenalinae Hydrochloridi.* **Syn.**—*Epinephrine Hydrochloride Solution.*—1 in 1000. To be kept in amber-coloured glass bottles. **B.P. Dose.**—2 to 8 ms. or 0.12 to 0.5 mil subcutaneously.

NON-OFFICIAL PREPARATIONS

1. *Unguentum Adrenalinae et Cocainae.* **B.P.C.**—Adrenaline 0.1 grm., boric acid 0.2 grm., cocaine hydrochlor. 1.0 grm., distilled water 3 mil; lanoline 50 grm., white soft paraffin 45.7 grm.

2. *Nebula Adrenalinae Aromatica.* **B.P.C.** **Syn.**—*Adrenaline Inhalant.*—Adrenaline $\frac{8}{10}$ grs., absolute alcohol $2\frac{1}{2}$ oz., eucalyptol 1 oz., oil of gaultheria 192 ms., hydrochloric acid *qs* to dissolve adrenaline, castor oil 10 oz., arachis oil to 20 oz. A soothing and astringent application to the nasal mucous membrane. To be used with an atomiser.

3. *Nebula Adrenalinae et Cocainae.* **B.P.C.**—Adrenaline chloride solution 4 oz., cocaine hydrochloride $87\frac{1}{2}$ grs., chlorbutol 35 grs., sodium chloride 63 grs., water to 20 oz. A sedative and hæmostatic.

4. *Suppositorium Adrenalinae.*—Contains adrenaline $\frac{1}{60}$ gr. in each. Those with cocaine contain $\frac{1}{4}$ gr. of cocaine in addition to above.

PHARMACOLOGY

The main action of adrenaline is stimulation of the sympathetic nerve-endings, both motor and inhibitory, except those of the sweat glands. It therefore produces effects on all the organs of the body.

Applied locally to mucous surface adrenaline causes blanching by powerfully constricting the capillaries of the part due to stimulation of the vaso-constrictor nerve-endings of the arterioles at the site of application. Given by the mouth it has no systemic effect, possibly by constricting the arteries it prevents its own absorption. The slow absorption helps the destruction of the drug in the stomach before it reaches the circulation. Although it is rapidly destroyed some hold that if retained in the mouth it is sufficiently

absorbed by the sublingual tissues to produce its systemic effects, chiefly rise of blood-pressure and dilatation of the bronchial muscles. This however is doubtful.

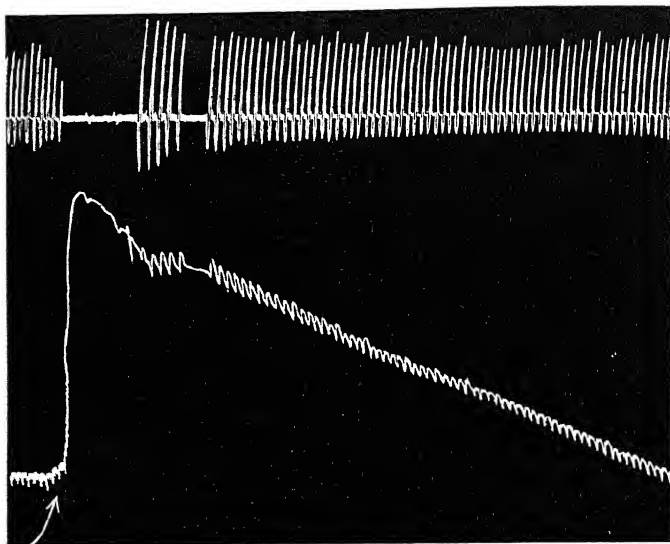


FIG. 9.—Anæsthetised Dog. Vagi intact.

Action of Adrenaline on Respiration and Blood-pressure. At point of arrow 0.5 c.c. of 1 in 100,000 solution of adrenaline was introduced into the femoral vein. Note the sudden rise of blood-pressure. Respiration is inhibited at first (adrenaline apnoea) and gradually returns to normal. This effect is reflex from rise of blood-pressure and not to respiratory depression.

Heart and circulation.—Injected intravenously it causes a rise of arterial blood-pressure. The pressure rises sharply and as it reaches the maximum the heart beats are strengthened and slowed. If the vagi are intact, as in normal animal, the rise is much less marked and is accompanied by definite slowing of the heart. Since the drug is quickly destroyed in the tissues, by the enzyme amine oxidase, the pressure is not sustained and returns to normal quickly. If a second injection is given when the pressure is already high it sometimes causes a fall instead of the usual rise. If the sympathetic myoneural junction is paralysed by the previous use of ergotoxine an injection of adrenaline causes a distinct fall of pressure (*see Ergotoxine*). The rise of pressure is due to constriction of arterioles from the direct action of the drug on the myoneural junctions in the muscular coat of the vessel walls and cardiac stimulation. The constriction is most marked in the smaller vessels, although the larger vessels and even the veins participate. The intensity of action depends upon

the relative preponderance of the sympathetic innervation and in the intact animal the main constrictor effect falls on the richly supplied splanchnic area, the skin and the kidneys and the minimum on the pulmonary and cerebral vessels. The coronary vessels are usually dilated, but very small concentrations cause contraction and diminish the flow of blood to the heart.

The heart is accelerated at first, then becomes slow, and finally becomes accelerated again. The quickening is the result of stimulation of the sympathetic endings in the heart muscle and is accompanied by more powerful contraction and complete emptying of the cavities. The slowing is due to excitation of the cardio-inhibitory centre in the medulla, and is due to stimulation of the centre by increased blood-pressure. As the coronary vessels are not constricted, rather dilated, the heart muscle gets more nutrition and the tone is improved, while its oxygen metabolism is also increased in proportion to its activity and rate. It has however the drawback of favouring the occurrence of fibrillation, specially when used before chloroform anæsthesia. In fact toxic doses produce auricular and ventricular fibrillation.

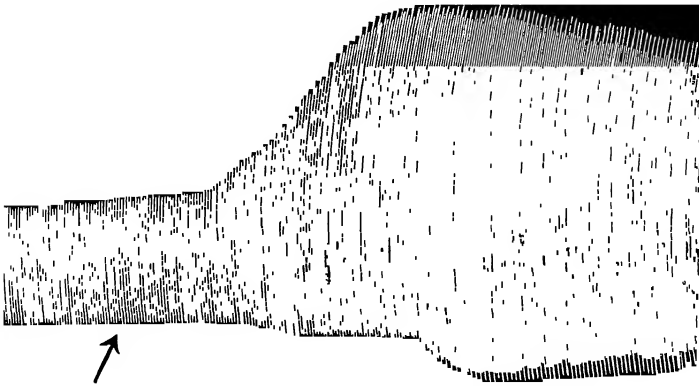


Fig.—10 Record of the movements of an isolated Rabbit's Heart during perfusion, showing effect of Adrenaline. Note the great acceleration and increased force of beat.

ye.—Solution of adrenaline dropped into the eye causes the conjunctiva to become pale and shrunken, the eyelids retracted, and makes the eyeball appear more prominent. Given intravenously it causes dilatation of the pupil by stimulation of the sympathetic nerve-endings.

Respiration.—During the height of blood-pressure follow-

ing an injection, the movements often cease or become shallow. This *adrenaline apnoea* (see fig. 9.) is a reflex effect caused by the rise of blood-pressure which stimulates the afferent nerve-endings in the aorta and in the sinus caroticus and is not produced after cutting of the vagi or denervation of the sinus caroticus. In small quantities used hypodermically it causes increased depth of respiration. Injected subcutaneously it causes relaxation of the bronchial muscles by stimulation of the broncho-dilator (sympathetic) nerve-endings.

Alimentary canal and liver.—Secretion of saliva is increased and corresponds in character with that due to stimulation of the cervical sympathetic. After an intravenous injection adrenaline stimulates the ends of the splanchnics (sympathetic nerves to the alimentary canal) and lessens peristalsis of the stomach and intestine, but increases the contractions of the pyloric, ileocaecal and internal anal sphincters which receive the augmentor fibres from the sympathetic. The movements of the gall-bladder are inhibited but those of the bile-duct are stimulated. Glycogenic function of the liver is disturbed causing unusual hydrolysis of glycogen with an excess of sugar in the blood and tissues, and if this exceeds the renal threshold will give rise to glycosuria.

Uterus.—Adrenaline causes contraction of the uterine vessels and of the uterus itself when pregnant. The effect however varies with the different species of animals and in the same species, whether pregnant or virgin. It usually relaxes the non-pregnant uterus of cat, but causes contraction during pregnancy. Surviving human uterus is stimulated whether pregnant or not (Lieb, 1915). It relaxes the force of contractions of the human pregnant uterus specially during labour. Clinically, a hypodermic injection of 0.5 c.c. of the liquor rarely causes any contraction, and abortion rarely follows when used for the relief of asthma in pregnant women.

Metabolism.—1.5 c.c. of 1 in 1000 solution given subcutaneously raises the basal metabolism by 20 p.c. in man.

Urine and sweat.—The vessels of the kidneys are contracted even in doses too small to influence the general blood-pressure. The secretion of urine is at first diminished but with the rise of pressure and subsequent relaxation of the renal vessels there is profuse diuresis, which continues for a little while even after the fall of the pressure. Urine often contains sugar due to an excess of sugar in the blood, *i.e.* it is antagonistic to insulin. Sweat glands though supplied by the sympathetic are not affected by it as the fibres are cholinergic (see page 222).

Toxic action.—(a) *Major symptoms*:—Acute dilatation of the heart with pulmonary oedema, ventricular fibrillation and death.

These usually follow intravenous injection if the heart is already weak and diseased.

(b) *Minor symptoms*:—These follow hypodermic use in susceptible persons. Palpitation, tachycardia, dyspnœa, rapid pulse, rise of blood-pressure, muscular tremors, nausea, vomiting, vertigo and cold sweats.

THERAPEUTICS OF ADRENALINE

The chief use of adrenaline is as a local hæmostatic, and intravenously as a circulatory stimulant in collapse and shock. Its action being of very short duration, it is suitable only in *emergency practice*, and is not employed in ordinary conditions of failure of compensation. It may be added to saline infusion where there is considerable loss of fluid, as in the treatment of cholera. In sudden stoppage of the heart in healthy persons, as for instance, in drowning and carbon monoxide poisoning, adrenaline injected directly into the heart may induce the heart to recommence beating, specially when accompanied with cardiac massage and artificial respiration. The intra-cardial injection should be given directly into the right ventricle, with a long fine needle, through the 4th intercostal space close to the sternum.

One of the effects of sympathetic stimulation is an improvement in conduction in the bundle of His; and beneficial results have been recorded in cases of complete heart-block in 5 to 10 ms. doses given subcutaneously. It lessens the Adams-Stokes attacks and is worth a trial. Since chloroform increases the output of adrenaline, it should not be used in cardiac failure associated with chloroform anæsthesia as it may precipitate fibrillation of the heart.

It has been employed with success as a local hæmostatic to all kinds of bleeding surfaces, as in epistaxis, bleeding gums, piles, metrorrhagia, etc., and on account of its property of constricting the arterioles it is often combined with cocaine or eucaine in eye lotions and nasal sprays. The prolonged use of adrenaline moreover as an eye lotion is apt to set up troublesome chemosis of the conjunctiva and lachrymation. As an internal hæmostatic it is useless.

It is often combined with cocaine and other local anæsthetics to prolong the effect of the latter, and at the same time to reduce the chance of bleeding and toxicity by retarding absorption. The usual concentration necessary is $\frac{1}{2}$ to 1 minim of the liquor in 20 minims of the solution (see page 260). Some patients suffer from palpitation, tremors, rapid pulse, etc., which however soon pass off and are due to idiosyncrasy. Moreover it has the drawback of producing local gangrene.

There is no satisfactory evidence that adrenaline is absorbed by the alimentary tract. This limits its use for oral administration to œsophageal spasm, gastrostaxis and vomiting, when it acts locally on the appropriate sympa-

thetic endings. It is also given to stop hiccough. Its use has been suggested in exophthalmic goitre, but the results obtained so far have not been very satisfactory.

As it relaxes the bronchioles it is especially valuable in **spasmodic asthma** when given hypodermically in $\frac{1}{2}$ to 1 c c. doses of the liquor. It is also used in urticaria, angioneurotic oedema, anaphylactic shock, hypoglycaemia following the use of insulin, and to prevent the occurrence of **nitritoid reaction** which may appear after the use of salvarsan and its derivatives.

Caution.—1. It should not be used at all, or used with caution in arterio-sclerosis where there is risk of sudden rise of blood-pressure.

2. In pulmonary or cerebral hæmorrhage there is risk of increasing the hæmorrhage.

3. In pulmonary oedema there is risk of increasing the oedema.

Mode of administration.—(a) *By mouth.*—For local action in the mouth and stomach. It appears to be rapidly destroyed before it can enter the general circulation. Sometimes sublingual administration is resorted to for the production of systemic effects.

(b) *Subcutaneously*, when there may be a slight rise in blood-pressure, but a marked effect on the contracted bronchi; but owing to intense local vaso-constriction, it is very sparingly absorbed and a very small dose may not produce any systemic effect. Sometimes severe palpitation and muscular tremor may follow its use.

(c) *Intramuscularly*, causes rise in arterial pressure and relaxation of the bronchi.

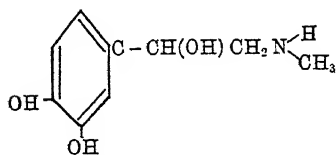
(d) *Intravenously*, causes immediate and marked rise in arterial pressure. The best method in collapse and shock. The intravenous dose should be about $\frac{1}{50}$ th of the hypodermic dose and should be given very slowly and freely diluted.

(e) *Intracardially*, in sudden failure of the heart (4-10 ms).

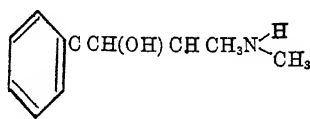
EPHEDRINE HYDROCHLORIDE

Ephedrine Hydrochloride. (Ephed. Hydrochlor.)

Source.—The hydrochloride of an alkaloid, ephedrine, obtained from *Ephedra sinica*, *Ephedra equisetina*, and other species of ephedra.



Adrenaline



Ephedrine

Characters.—Colourless crystals; odourless. *Soluble* in water and alcohol (90 p.c.). Aqueous solution neutral to litmus.

B.P. Dose.— $\frac{1}{4}$ to $1\frac{1}{2}$ grs. or 0.016 to 0.1 grm.

NON-OFFICIAL PREPARATIONS

1. **Elixir Ephedrinæ Hydrochloridi, B.P.C.**—Contains $\frac{1}{4}$ gr. ephedrine hydrochloride in each dl. *Dose*— $\frac{1}{2}$ to 2 dl. or 2 to 8 mls
2. **Nebula Adrenalinæ et Ephedrinæ, B.P.C.**—Solution of adrenaline hydrochloride, $2\frac{1}{2}$ oz., ephedrine hydrochloride 200 grs., glycerin of phenol, 200 ms., cinnamon water, q.s. 20 oz
3. **Tinctura Ephedra.**—Contains ephedrine and pseudo-ephedrine $\frac{1}{2}$ gr. in 60 ms. *Dose*—30 to 60 ms. or 2 to 4 mls

PHARMACOLOGY

Ephedrine is phenyl-methyl-amino-propynol, which is closely related to adrenaline and tyramine. Its action resembles adrenaline, the effects being produced from stimulation of sympathetic nerve-endings. In large doses it has various other effects, which have been ascribed to an indiscriminate stimulation of smooth muscle and to stimulation of autonomic nerve ganglia.

It is not absorbed by the unbroken skin, but is absorbed from mucous surfaces, stomach and rectum. The absorption however is slow and the effects last longer than adrenaline. It is a more stable compound, due to the fact that ephedrine is immune to enzyme amine oxidase, which normally destroys adrenaline, and its solution can be sterilised by boiling.

Just as eserine acts by inhibiting the action of cholinesterase and prolongs the action of acetyl-choline, ephedrine increases the action of adrenaline in much the same way by inhibiting the action of amine oxidase*.

Eye.—A solution of ephedrine dropped into the eye causes slight mydriasis without affecting accommodation or increasing the intra-ocular tension, and producing little effect on the conjunctival vessels. All these effects are due to stimulation of the sympathetic myoneural junction, and are elicited by 1 to 5 p.c. solution.

Heart and circulation.—Administered by the mouth or hypodermically it stimulates the myoneural junctions of the sympathetic in the heart and the vaso-constrictors, but less powerfully than adrenaline, causing **acceleration of the heart and rise of blood-pressure**, which is more prolonged. The rate however becomes slow with the rise of pressure. *The heart muscles are directly depressed* but is not marked in ordinary doses, being overcome by the accelerator effect. In large doses the depression is marked. The rise of blood-pressure is not proportional to the dose and becomes less with successive doses, and eventually falls, possibly due to depression of the cardiac muscle (Chen).

* Gaddum, *British Medical Journal*, April, 2 1938

Pseudo-ephedrine has action similar to ephedrine but weaker, it is however a direct stimulant to the heart.

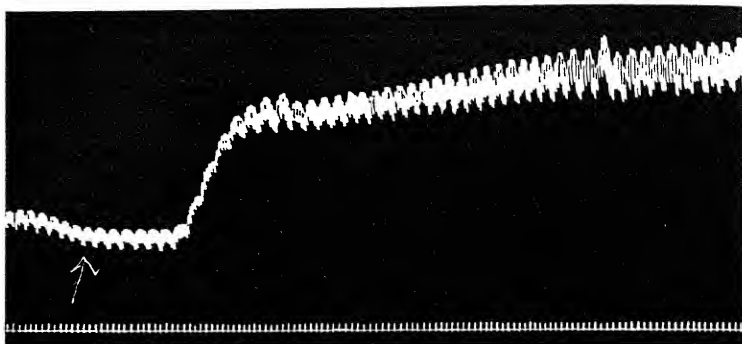


Fig. 11.—Dog 4 kilo. 0.75 c.c. of 0.3 p.c Ephedrine Hydrochloride. Showing the effect of Ephedrine on Blood-pressure. Note the prolonged effect. Compare fig.12 showing effect of adrenaline and ephedrine in contrast.

It increases the red cells and leucocytes due possibly to extrusion into the circulation of erythrocytes, leucocytes and platelets from the storage and hæmopoietic centres including the bone marrow.*

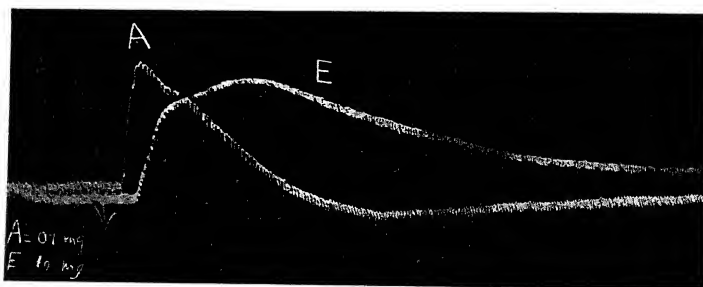


Fig. 12.—Anæsthetized cat. A, adrenaline; E, ephedrine. Showing effects of adrenaline and ephedrine on blood-pressure in contrast.

Respiration.—It stimulates the respiratory centre, and relaxes the bronchial muscles specially when constricted as in asthma, or after physostigmine. This effect is due to its action on the broncho-dilator (sympathetic).

It stimulates the central nervous system and large doses produce insomnia, tremors and anxiety reflex specially in women. It does not reduce the secretions, and some observers claim that it stimulates the intestinal muscles which are depressed by adrenaline, while others report that its effect

*Simpson and Cadness; *Journal of Pharmacology*, 1936.

on the gut muscle is the same as adrenaline. The uterus contracts in all animals, but is less sensitive to this drug than adrenaline.

THERAPEUTICS

Ephedrine is used in the same conditions where adrenaline is indicated. In bronchial asthma it gives relief within 20 to 30 minutes when administered by the mouth in $\frac{1}{4}$ to $\frac{1}{2}$ gr. doses, and given two to three times a day it will keep away the attacks. It is not so potent as adrenaline in severe attacks, and very soon toleration is induced, and a larger dose

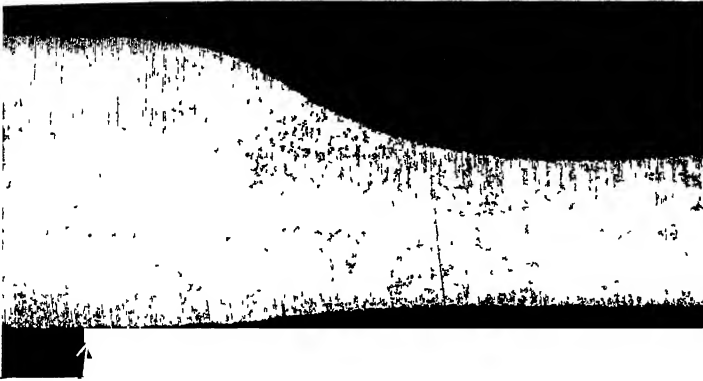


Fig 13—Record of the movements of Isolated Rabbit's Heart perfused with Locke's solution showing effect of Ephedrine. At the point of arrow a small dose of ephedrine was administered. Note depression of the heart with weakening of contraction.

is required to produce the same result. Some patients complain of severe sweating and sleeplessness, while others show no effect after a single dose of $\frac{1}{2}$ gr. It relieves whooping cough, specially during the second stage, when given in $\frac{1}{8}$ to $\frac{1}{4}$ gr. doses twice a day to children 1 year old.

It is used in anaphylactic shock, hay fever, urticaria and in angio-neurotic oedema, and as an addition to local anæsthetics in place of adrenaline. It counteracts the collapse which follows the use of spinal anæsthesia. In hay fever it acts both when given by the mouth and as a nasal spray (3 to 5 p.c.), when it causes shrinkage of the engorged mucous membrane. This effect has been found useful in the treatment of cold and has been utilised in nasal surgery.

Because it stimulates the respiratory centre it is used in narcotic poisoning, and is superior to caffeine, strychnine, and even carbon dioxide (Chen).

It is also useful in *yasthenia gravis* when $\frac{3}{4}$ gr. daily causes progressive increase in strength by the retention of

creatine in the muscle; and lessens the tremor and weakness in post-encephalitic parkinsonism.

Because of its stimulating effect on the central nervous system it may be used to prevent pathological sleep in **narcolepsy**, a condition characterised by drowsiness when inactive.

By improving the tone of the sphincter of the bladder it improves **nocturnal incontinence of urine** in children when given in $\frac{1}{2}$ gr. doses at bed-time to a child 10 to 12 years old.

Its use has been recommended in complete **heart-block** and Gilchrist* used it in $\frac{1}{2}$ gr. doses in this condition with Stokes-Adams' syndrome three times a day. It relieves nerve pain in leprosy better than injections of adrenaline.

As it contains some pseudo-ephedrine, the tincture is used as a **stimulant** to the heart in pneumonia, asthenic conditions, low blood-pressure, etc.

Toxic symptoms.—Large doses cause tachycardia, tremors, vertigo, palpitation, sweating, nausea and irritation of the bladder with difficulty in passing urine and fæces. They are associated with high blood-pressure and disappear when it returns to normal. The chief danger is cardiac depression and it should not be used in cardiac asthma, when the heart is damaged, and in acute circulatory collapse.

Some patients are specially sensitive to ephedrine and even a small single dose ($\frac{1}{2}$ gr.) given for the relief of asthma or urticaria produces symptoms of collapse, perspiration, tremor, palpitation, etc. It causes euphoria in some people.

EPHETONIN (Not official). *Syn.*—*Synthetic Ephedrine*.—A hydrochloride of *phenylmethylaninopropanol*. Closely related to ephedrine and has properties similar to ephedrine or adrenaline. Given orally in the same conditions where adrenaline is indicated. Supplied in tablets of $\frac{1}{4}$ gr. each and in ampoules for hypodermic injection.

EN E IN

(Not official)

Benzedrine or *p*-phenylisopropylamine is chemically allied to adrenaline and ephedrine. Occurs in colourless liquid which volatilises readily in ordinary temperatures. When exposed to air it absorbs carbon dioxide and forms a carbonate which also readily volatilises.

PHARMACOLOGY AND THERAPEUTICS

Its action resembles adrenaline or ephedrine and is a stimulant to the sympathetic system. It raises the blood pressure without any effect on the pressure of spinal fluid, paralyses intestinal activity, and powerfully stimulates the higher portions of the central nervous system giving rise to increased energy and capacity for work, and a feeling of well-being. It may cause pronounced psychological effects which are characterised by increased confidence and initiative, ease in making decisions, and inclination to talk more than usual. There may be restlessness which may be pleasant or unpleasant. It causes a rise of red and white cells due possibly to contraction of the spleen.

* *British Medical Journal*, April 7, 1934.

When inhaled it causes local vaso-constriction and is used in hay fever, acute coryza, and in all catarrhal conditions of the respiratory system. For this purpose it is available in the form of inhaler, which consists of benzedrine 0.325 grm. with oil of lavender and menthol.

In the form of tablets ($\frac{1}{4}$ to $\frac{1}{2}$ gr. or 10 to 30 mg.), Benzedrine Sulphate is administered internally, and its use has been recommended in shock, fatigue, nervous exhaustion, and spasm of the involuntary muscles, as asthma, colic, pyloric spasm, etc. It is of value in post-encephalitic parkinsonism specially when drowsiness and lack of energy predominate, and is more effective when combined with scopolamine or stramonium.

It is largely used in mental disorders, for preventing narcoleptic attacks, and in various forms of psychoneuroses to prevent fatigue.

As it increases the secretion of hydrochloric acid and pepsin it may be of value in differentiating functional from organic achlorhydria.

Untoward symptoms.—These may be physical or psychological. Difficulty in passing urine and fæces, loss of weight, skin rash, rise and sometimes paradoxical fall of pressure, and transient heart-block.*

Contra-indications.—Hypertension, coronary artery disease, maniac excitement.

2. Drugs Lowering the Blood-pressure

Vaso-dilators

Vaso-dilators are drugs which dilate the arterioles and lower the blood-pressure; they act in the following ways:—

1. *Depressing the vaso-motor centre.*—Narcotics, chloroform and ether anaesthesia.

2. *Depressing the sympathetic nerve cells.*—Nicotine, codeine, apocodeine.

3. *Depressing the plain muscles of the vessels.*—Nitrites, acetyl choline, theobromine.

4. *Paralysing the capillaries.*—Histamine, arsenic in poisonous doses.

5. *Depressing the vaso-motor nerve-endings.*—Ergotoxine in large doses.

A MYL NITRIS

Amyl Nitrite. (Amyl. Nitris)

Source.—Prepared by the esterification with nitrous acid of the fraction of fusel oil (which distils between 128° and 132°). Contains not less than 90 p.c. of nitrites, calculated as $C_5H_{11}O_2N$. Consists chiefly of the nitrites of *iso*-butylcarbinol, and *sec*-butylcarbinol, with other nitrites of the homologous series.

Characters.—A clear, yellow liquid; odour, fragrant; taste, pungent and aromatic; sp. gr. 0.874 to 0.884; *very volatile*. *Solubility.*—Soluble in alcohol (90 p.c.), insoluble in water.

Dispensing hints—It should be kept in hermetically sealed bottles in a cool, dark place. Agitation or heat helps evaporation.

B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil by inhalation.

PHARMACOLOGY

Externally.—Amyl nitrite is a direct local depressant to the sensory nerves, but the action is transitory.

Internally. Blood.—It enters the blood readily through the lungs and stomach, and circulates as sodium nitrite. If absorbed in sufficient quantity, it converts the hæmoglobin into methæmoglobin and another body—nitric oxide hæmo-

* Davies, *British Medical Journal*, Sept 25, 1937.

globin—and renders the arterial and venous blood chocolate-coloured, and thereby interferes with the oxidising property of the corpuscles. In ordinary doses the effect is slight and the methæmoglobin is soon deoxidised, but in toxic doses these changes are enough to cause death. The inhalation of oxygen soon reconverts methæmoglobin.

Heart and blood-vessels.—Within a minute of inhalation, the face, head and neck become warm and flushed, the carotids and their branches throb, head feels full and tense, and the heart beats rapidly and violently, soon followed by headache, giddiness, rapid breathing and dilatation of the pupils. All these effects are due to dilatation of the vessels of the head and neck (blush area). But very soon the vessels of the whole body dilate with enormous fall of blood-pressure. The vaso-dilatation is due to direct action of the nitrite on the vessel walls and not to any effect on the vasomotor centre. The blood-pressure does not fall if the nitrite is introduced into the cerebral circulation and prevented from reaching the peripheral vessels. On the other hand there is vaso-dilatation after ligature of the vessels to the brain, after destruction of the spinal cord, and when applied to excised organs or arterial segments. The dilatation is more marked in the splanchnic area and the extremities. The coronary, pulmonary and cerebral vessels also dilate, but the blood supply to the heart is reduced.

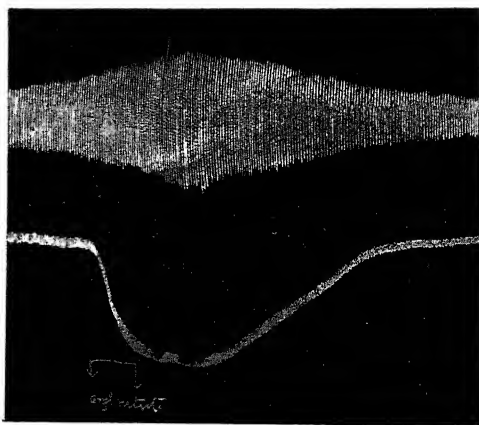


FIG. 14.—Dog. Respiration and Blood-pressure.

At point of arrow amyl nitrite was given by inhalation. Note fall of blood-pressure and stimulation of respiration which becomes quicker and deeper.

After inhalation there is at first slight slowing of the heart due to reflex vagus stimulation. Very soon however

the rate quickens from depression of the vagal centre both directly and from fall of pressure. The heart muscle shows no important change, but the improved coronary circulation and lowered peripheral resistance may improve and relieve a weak heart. Large doses however depress the heart and make it weak and slow.

Muscles —The activity of most of the involuntary muscles is depressed, but the effect on arterial muscles is most marked. The muscles of the bronchioles, uterus and intestine also become relaxed.

Lungs.—Respiration is at first quickened by stimulation of the respiratory centre through diminished supply of blood to the brain as a result of the fall of blood-pressure. Later on it becomes laboured and difficult, and finally ceases altogether when the centre becomes asphyxiated. The bronchial muscles are relaxed.

Nervous system.—When inhaled for a short time and in small quantities it has very little effect on the higher parts of the central nervous system. But the medullary centres may be slightly stimulated at the beginning reflexly from irritation of the sensory terminations of the nasal mucous membrane. But with the fall of blood pressure and consequent anæmia of the medulla the activity of the inhibitory centre for the heart is depressed and both the respiratory and vasomotor centres are stimulated. Most of the nervous symptoms such as headache, giddiness, throbbing in the head, etc., are due to the dilatation of the arterioles and fall of blood-pressure. The function of the sensory and motor nerves is affected a few minutes before death.

Eye.—There is a temporary blurring of the sight as a result of the dilatation of the retinal vessels, dilatation of the pupil and increase of intra-ocular tension.

Temperature.—Under the influence of amyl nitrite the temperature falls both in health and fever, due to peripheral vascular dilatation, although the surface temperature may be increased from dilatation of the skin vessels.

Excretion.—It escapes with the urine as nitrites and nitrates, but the quantity is less than what is absorbed, about 60 to 70 p.c. disappearing in the body. Its diuretic action is uncertain and depends upon whether the renal vessels or those of the general circulation are relatively more dilated.

THERAPEUTICS

Inhalation —The profession first learned the use of amyl nitrite in *angina pectoris* from Brunton, who, seeing that it dilated the arterioles, used it in this disease with startling effects. Since anginal attacks may occur without a corresponding rise of blood-pressure its action is possibly due to relaxation of the coronary spasm. Five drops give speedy relief, especially if the disease is paroxysmal. It may even

afford relief to angina when there is no vaso-motor contraction. In fact, it relieves, though temporarily, any **cardiac pain** of a paroxysmal nature, but its action is of such fleeting nature as to render it useful only in emergency and should be followed during the interval of attacks by sodium nitrite or nitroglycerin. The pain of thoracic aneurism is often allayed by it. The "flushing" or "heat" which many women experience during the menopause may be controlled by this drug. It may arrest a fit of epilepsy if inhaled as soon as the aura is perceived. In migraine due to spasm of the blood-vessels of one side of the face, as indicated by the paleness of the affected side, inhalation of amyl nitrite gives relief. It has been found useful in **syncope** and **fainting**. Its use has been suggested in collapse of chloroform anaesthesia, but since in this condition the heart is extremely depressed and the arterial pressure is considerably low, the use of amyl nitrite will lower the pressure still further which may be enough to stop the heart.

On account of its action in lowering blood-pressure its use has been advocated in **hæmoptysis** on the idea that it will help formation of clot at the point of injury, and in urgent cases we have often found it to give valuable results.

It has been found efficacious in uncomplicated **asthma**, relieving dyspnoea within a short time. It also temporarily affords relief to **cardiac dyspnoea** by lowering the pressure of the systemic arteries. It may relieve the pain of dysmenorrhœa and relax uterine spasms.

Caution.—It should be used with great caution in sensitive and nervous persons, who are powerfully affected by it. It should not be administered to persons suffering from aortic diseases, advanced degeneration of the cardiac muscle, those whose arteries are atheromatous, or to those who are emphysematous, plethoric or suffer from chronic bronchitis.

Prescribing hints.—Inhalation is the usual method. The drug may be poured on a handkerchief, or a glass capsule broken within its folds and inhaled. The glass capsules keep better in India. Patients may become habituated to its use, so that after a while it has to be inhaled several times before it will give relief.

LI U GLYCE YLIS T INIT ATIS

(Liq. Glyc. Trinit.)

Solution of Glyceryl Trinitrate

Syn.—Solution of Nitroglycerin; Spiritus Glycerylis Nitratis; Liquor Trinitrini.

Source.—A solution of glyceryl trinitrate, in alcohol (90 p.c.) containing 1 p.c. w/v of $C_2H_5(NO_2)_3$, or $\frac{1}{75}$ gr. in 2 ms.

Characters.—A clear, colourless liquid, neutral to litmus. Sp. gr. 0.836 to 0.841.

B.P. Dose.— $\frac{1}{2}$ to 2 ms. or 0.03 to 0.12 mil.

OFFICIAL PREPARATION

1. *Tabella Glycerylis Trinitratis* *Syn.*—*Tabellæ Trinitrim*; *Nitro-glycerin Tablets*.—Each contains 0.0005 grm. or $\frac{1}{1000}$ gr. of Glyceryl trinitrate. B.P. Dose.—1 or 2 tablets.

YTH ITHYLIS TET ANIT AS ILUTUS

(Erythrityl. Tetranit. Dil.)

Diluted Erythrityl Tetranitrate

Syn.—Erythrol Tetranitrate (50 p.c.).

Source—A mixture of approximately equal weights of erythrityl tetranitrate and lactose. Contains 47.5 to 52.5 p.c. of $C_4H_6O_{12}N_4$.

Characters—A white powder; odourless; tasteless, except for the slight sweet taste of lactose. Partially *soluble* in water, and in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to 2 grs. (representing $\frac{1}{4}$ to 1 gr. of pure erythrityl tetranitrate) or 0.03 to 0.12 grm. (representing 0.015 to 0.06 grm. of pure erythrityl tetranitrate).

PHARMACOLOGY AND THERAPEUTICS

Nitroglycerin is absorbed unaltered by the stomach, but on reaching the blood it is decomposed into glycerin, nitrites and nitrates. Its action is the same as that of amyl nitrite but the effects though not so prompt, are more lasting than those of amyl nitrite. Administered under the tongue its absorption is more rapid than when swallowed. In fact sublingual administration is adopted for prompt effect and in preference to amyl nitrite in the treatment of **angina pectoris**. Generally nitroglycerin is given in the intervals of attacks every four or six hours to prevent further attacks, and amyl nitrite is reserved for administration during the actual onset of the paroxysm. One of the drawbacks to the use of this drug is that it is apt to cause a severe throbbing headache. This may be avoided by breaking up each tablet into eight or more portions, and to take one of these portions every 15 or 20 minutes during the day. Since nitroglycerin is not wholly broken up in the system it has been suggested that the headache is due to the undecomposed molecule and not to the nitrite constituent. Patients rapidly become habituated to nitroglycerin.

Although it has no direct action on the heart its use has been advocated in different forms of cardiac diseases, and the benefit which follows its use is indirect due to vascular dilatation which decreases the resistance against which the left side of the heart is working. On the other hand its use is contra-indicated in advanced heart disease where the heart muscles are degenerated. Here the blood-pressure is already low and any further reduction of the pressure will not only lead to syncope from anæmia of the brain, but a low coronary pressure will also lessen the nutrition of the heart and still further weaken the muscle.

It is largely used for the purpose of lowering supernatural blood-pressure, but the general experience of clini-

cians is that the drugs of this group often fail to produce any permanent lowering of pressure.

It will often prevent sea-sickness, and if the treatment be commenced after sickness has already occurred, the patient may continue to vomit but the horrible feeling of nausea and depression disappear and the physiological effect of the drug does not occur. It must be given cautiously, and for administration to delicate persons or children the treatment should be commenced with a dose of $\frac{1}{200}$, $\frac{1}{400}$, or $\frac{1}{800}$ gr.

It is as a rule a perfectly safe drug and even children have taken large doses without ill effects.

Erythrol tetranitrate has a more prolonged action than amyl nitrite or nitroglycerin, but it is more expensive.

S II NIT IS

Sodium Nitrite. (Sod. Nitris). NaNO_2

Source.—May be obtained by reducing sodium nitrate with metallic lead. Contains not less than 95 p.c. of pure sodium nitrite.

Characters.—Colourless, or slightly yellow, crystals, or a white, or slightly yellow granular powder. Taste, saline. Deliquescent. Soluble in 1.5 parts of water.

E.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

PHARMACOLOGY AND THERAPEUTICS

Sodium nitrite possesses properties similar to amyl nitrite and nitroglycerin, but it is slower in its action than the former and does not cause so much throbbing and headache as the latter. It is used in angina pectoris, aortic disease, and in the increased arterial tension which accompanies granular kidney. It has been used with success in hemi-crania, and in bronchial asthma. In the air it gradually oxidises to nitrate and loses its efficacy. Given during the digestive period, *i.e.* while there is free hydrochloric acid, it sets free nitrous acid, which is not only irritating to the stomach but may be partly oxidised and rendered inert before absorption.

For asthma, it is given combined with hyoscyamus in doses of 1 to 3 grs. frequently repeated.

GROUP VII

DRUGS ACTING ON THE RESPIRATORY SYSTEM

There is an intimate relation between the respiratory organs, the external air, the blood, the circulation, the nervous system and the respiratory centre. A disturbance in any one of them at once reflects upon the respiratory mechanism. The chief function of respiration is to supply oxygen to the tissues and to excrete CO_2 , and this oxygen requirement and CO_2 excretion are proportional to the degree of activity of the body. This gaseous exchange in the lungs and the tissues takes place according to the physical law of diffusion of

gases, i.e. the gas diffuses from a point of high tension to one of lower tension till equilibrium is established, when the diffusion becomes equal in both directions. Any failure of respiration is accompanied by deprivation of oxygen and accumulation of CO_2 .

The complex process involved in respiratory movements is controlled by the *respiratory centre* situated in the pons and upper part of the medulla at the level of the *calamus scriptorius*. Although sensitive to various reflex stimulation, the centre is autonomous. It is possible that there are two centres, one normally concerned is the *inspiratory centre* which co-ordinates the inspiratory muscles concerned in the respiratory movements; the expiration being purely passive, the centre for expiration is not brought into activity except under special circumstances. The impulses of both inspiration and expiration for the entire respiratory mechanism are distributed in a co-ordinated way to the lower motor centres in the cord, and in the case of nose and larynx to the motor centres of the vagus and facial.

The vagus is the chief nerve of respiration, containing both sensory and motor fibres, and therefore plays a most important part in respiratory functions. The afferent filaments, which abundantly supply the wall of the air passages and probably the lungs, constantly transmit impressions to the centre and modify respiratory movements. Again, the muscles of the bronchi being supplied with the efferent fibres of the vagus, are constantly affected by various afferent impressions which may even arise in the air tubes themselves. Besides the vagus afferent nerves passing from the carotid sinus and aortic arch are actively concerned with the regulation of breathing. The afferent fibres from the laryngeal mucous membrane are concerned with the cough reflex which guard the respiratory passages against the entrance of foreign bodies.

The respiration is also influenced by variations in the blood-pressure. A rise in the pressure in the resting animal depresses respiration while a fall stimulates breathing. This effect is reflex, the rise of pressure stimulating the sensory endings in the aortic arch (supplied by the sinus nerve, a branch of the glosso-pharyngeal).

Apart from the nervous control, the centre is highly sensitive to the conditions of the gases in the body. If the blood becomes more venous, the centre is stimulated and the respiratory movements augmented both in rate and force. Conversely, if the blood is more oxygenated by free ventilation of the lungs, or the tension of CO_2 is diminished, the centre acts more feebly, or may fail to act giving rise to a condition known as *apnoea*. The centre therefore is stimulated when the CO_2 tension of plasma is increased. The CO_2 combines with water and forms carbonic acid, H_2CO_3 , which dissociates to yield H-ion thus increasing the hydrogen-ion concentration of the blood which stimulates the centre. Respiration therefore is very sensitive to the slightest change in the hydrogen-ion concentration of the blood and responds in such a way as to keep the reaction at its normal level. Similarly after exercise a large amount of carbon dioxide is discharged into the plasma increasing its hydrogen-ion concentration which stimulates the respiratory centre resulting in augmented breathing, by which the excess of CO_2 is removed and more oxygen is absorbed to supply the muscles. Just as increased tension of carbon dioxide stimulates the centre so a lack of oxygen, though it does not directly stimulate the centre, makes it more sensitive to CO_2 . If the deficiency of oxygen is not associated with increase of CO_2 the increased breathing will only eliminate more CO_2 thus reducing the hydrogen-ion concentration of the blood (alkalosis). Lack of oxygen is known as *anoxæmia*, and the symptoms develop as the supply of oxygen becomes deficient.

Besides the above factors, breathing is also influenced by the higher centres; by the sensory impulses from the body surface, e.g. painful and thermal stimuli; during swallowing when the breathing

becomes inhibited by impulses coming from the glosso-pharyngeal nerves from the post pharyngeal walls; and during sleep, when the centre is depressed.

Drugs stimulating the respiratory centre.—We have already seen that alteration in the composition of the air inhaled and excess of carbon dioxide affect the respiratory centre. Any cause which tends to diminish the oxygenation of the blood, *e.g.* hæmorrhage, or deficiency of hæmoglobin as in anæmia or when brought about by certain drugs, stimulates the centre and increases the respiratory movements. In the same way iron, arsenic and liver extract by increasing the hæmoglobin of the red blood-cells improve respiratory distress. The centre may be stimulated by certain drugs, specially strychnine, ammonia, caffeine, atropine, ephedrine, carbon dioxide gas, lobeline, camphor and apomorphine. Substances which stimulate the central nervous system also stimulate the respiratory centre. Finally the centre may be stimulated reflexly through sensory stimulation, *e.g.* inspiration caused by application of cold to the body, inhalation of ammonia vapour or smelling salts.

Drugs depressing the respiratory centre.—The respiratory centre is more easily depressed than any of the other vital centres. In fact in most of the fatal diseases there is respiratory depression before death. Respiratory depressants make the centre less sensitive to carbon dioxide. Anæsthetics, hydrocyanic acid, aconite, gelsemium, etc., depress the centre. Morphine, heroin, chloral are powerful in this respect. The cough centre being closely related to the respiratory centre, respiratory depressants also depress the cough centre and are used to check excessive coughing.

The drugs acting on the Respiratory System are:—(a) *Respiratory stimulants*; (b) *expectorants*, or drugs which increase or liquefy the bronchial secretion and help its expulsion; (c) *bronchial antispasmodics*, or remedies which relieve respiratory spasms chiefly by relaxing the bronchial muscles; (d) *respiratory sedatives*, which allay cough and reduce excessive secretion, *e.g.* opium and drugs of the belladonna group; and (e) *pulmonary antiseptics*, or remedies which when inhaled, or when used internally, during excretion, act as antiseptics.

CLASS A: Carbon Dioxide, Oxygen

CA NEI I XI U

Carbon Dioxide. (Carbon. Diox)

Source.—May be obtained from mineral carbonates, or from the fermentation of sugars. For convenience it may be compressed in metal cylinders.

Characters.—A heavy, colourless gas. One volume of gas dissolves in about 1.3 volumes of water at 25°C.

NON-OFFICIAL PREPARATION

1. **Carbon Dioxide Snow**—It is obtained by sudden release of liquid carbon dioxide contained in cylinders under a pressure of about 50 atmospheres. It has a temperature of -80°C. The solid snow is moulded into proper shape to suit the part which it is desired to treat. It is applied with slight pressure for from five to six seconds according to the effect desired. A short application of a few seconds causes blanching followed by hyperæmia, while prolonged application acts as a caustic and destroys diseased cells.

PHARMACOLOGY AND THERAPEUTICS

In the form of effervescent preparations CO₂ is extensively used in medicine, and many mineral waters and aerated waters contain CO₂ gas.

Locally applied, the gas or its solution, acts as a mild irritant to the skin and mucous membrane, and if the application is prolonged it is followed by numbness and anæsthesia. This sensory irritation leads to reflex stimulation. Carbon dioxide bath (Nauheim bath) is therefore used in many conditions of nervous and circulatory weakness, and in different diseases of the heart. Applied as a pencil (carbon dioxide snow), it not only causes anæsthesia by local freezing but also destroys the superficial tissues. It is therefore used as a mild caustic for superficial growths like warts, nævi, lupus, rodent ulcers, etc., in preference to other caustics.

Internally —The mild irritant effect is also noticed when the gas is taken internally. In the stomach it acts as a stomachic by increasing its vascularity and secretion; it also helps expulsion of gas and acts as a carminative. Aerated water is more quickly absorbed than ordinary water and having a sharp taste is more freely taken. It is therefore a valuable diuretic and can be used when rapid flushing of the system is desired. Being sedative to the stomach, aerated water, or carbonic acid gas in an effervescent mixture, may be used in vomiting, sea-sickness, etc.

Except when the gas is inhaled it produces no systemic effect when taken by the mouth, being mostly expelled out from the stomach by eructation. Very little is absorbed and is excreted by the lungs, and it does not alter the normal CO_2 content of the blood.

When inhaled in pure form, it causes asphyxia like any other indifferent gas, due partly to its effect on the central nervous system and partly to anoxæmia. Inhaled mixed with oxygen, it causes a rise of blood-pressure, first stimulates and then depresses the respiratory, vaso-motor and vagus centres. A concentration of 5 p.c. directly stimulates the respiratory centre. By stimulating the sensory nerve-endings in the carotid sinus region and the aortic arch, it sends excitatory impulses to the respiratory centre so that CO_2 also stimulates the centre reflexly. The effects however disappear with the supply of fresh air. Stimulation generally follows the use of a concentration of $8\frac{1}{2}$ p.c., whereas a high concentration (20 to 30 p.c.) causes depression and paralysis of the vaso-motor centre and the heart. Normally the respiration is regulated by the CO_2 content of the blood and the centre is sensitive to slight increase of CO_2 tension. Inhalation of oxygen with 5 p.c. CO_2 has therefore been used to stimulate the respiration and the vaso-motor centre in carbon monoxide poisoning, chloroform and ether anæsthesia and in narcotic poisoning. In chloroform and ether anæsthesia it stimulates breathing and accelerates absorption, thus hastens induction of anæsthesia; given after operation it ensures hyperventilation and deep breathing and thus helps elimination of the anæsthetic and diminishes the risk

of post-anæsthetic complications, viz. nausea and bronchitis. It has been used successfully to control hiccough (30 p.c. of CO₂ to 70 p.c. of oxygen).

5 to 10 p.c. carbon dioxide in pure oxygen is a valuable means of raising the blood-pressure in spinal anæsthesia provided the motor nerves of respiration are not also paralysed, when artificial respiration and vaso-constrictor stimulants are of service.

It has been used in asphyxia of the new-born, drowning, and in alcoholism to hasten excretion by the lungs.

OXYGENIU

Oxygen

Source.—Prepared by the fractional distillation of liquid air, or by the electrolysis of water. Contains not less than 98 p.c. v/v of O₂. For convenience it is compressed in metal cylinders.

Characters.—A colourless, odourless and tasteless gas. One volume dissolves in about 43 volumes of water, and in 3.6 volumes of alcohol (95 p.c.).

ACTION AND USES

Oxygen, though present in small proportion (20 p.c.) as compared to nitrogen, is the most important constituent of air. An increase of this proportion or even inhalation of pure oxygen produces no noticeable effect under normal conditions, and the oxidation in the tissues is not increased nor metabolism modified, but tends to raise the blood-pressure and causes a slowing of the heart by causing sinus bradycardia. It has however a distinct value in cases where the tension of oxygen in the alveolar air is low or there is interference in the passage of oxygen through the alveolar wall, so that oxygen tension in the blood is below normal. At high altitudes the atmospheric oxygen tension is less and there is increased formation of red blood-cells and increased anabolism in other tissues specially the muscles.

The function of oxygen therapy is not to attack the underlying causes of the disease, but to give the patient the benefit of as high a blood oxygen saturation as possible. It is no doubt possible that some of the benefits of oxygen therapy may be obtained by other therapeutic measures apart from the improvement of arterial anoxæmia.

When hæmoglobin of the blood is so altered as to be incapable of carrying oxygen to the tissues, as for instance, in poisoning by carbon monoxide, nitrites, chlorates, etc., inhalation of oxygen may be of some benefit. It is useful in those forms of asphyxia due to the interference with the access of oxygen to the blood, e.g. in pneumonia (due to diminished absorbing surface of the lung), croup, drowning (due to mechanical interference with respiration), in collapse of anæsthesia (due to depressed respiration), etc. Similarly

it is useful when there is deficiency in the actual quantity of hæmoglobin, as in certain forms of anæmia. Here it increases the oxygen carried in solution by the plasma and not by increasing the quantity of oxygen carried by the hæmoglobin. It is also useful in advanced heart disease when the supply of oxygen to the tissues is impaired from circulatory failure; in anoxic conditions, as may occur in mountain sickness due to insufficient pressure of oxygen in the inspired air; and in pulmonary oedema.

It is of undoubted value in **coronary thrombosis**. A concentration of 50 p.c. will aid in maintaining an adequate oxygen supply to the tissues of the body until the heart has had an opportunity to recover from its functional disturbance.

Mode of administration.—For therapeutic purposes oxygen can be obtained in cylinders, and the simplest way is to pass the tube connected with the cylinder through water and then deliver through a glass funnel which is held near the patient's nose, or put into the mouth or into the nose by a rubber catheter with extra holes at the top. The catheter should be adjusted to the comfort of the patient and fixed in place with adhesive tape. Sometimes a large rubber bag is fixed in the tube to prevent the gas from issuing with too much force. In order that oxygen may be of any use, it is necessary that it should be given before any marked signs of cyanosis appear when giving to patients suffering from pneumonia. Ordinarily three bubbles a second when passed through water yield 0.2 litre per minute. When held before the nose much of the oxygen is wasted and the air becomes enriched by 3 to 5 p.c. Subcutaneous injection is considered by French physicians as the route of choice, and it is claimed that when given by this method the effects are more pronounced, as a definite amount is supplied to the system promptly.

Method of subcutaneous injection.—In emergencies it can be supplied by connecting the outlet tube with a hypodermic needle, and introducing the gas into the tissues by pressing the rubber bag. This method is slow and the amount of oxygen introduced is uncertain. It may be introduced by a special apparatus. The outer aspect of the thigh or abdomen is the part selected for injection. After the usual aseptic precautions, the needle is inserted through the skin and tissues between the fascia and the lower surface of the dermis, avoiding the subcutaneous fat as much as possible. Formation of an even swelling of tissue or of small bubbles appearing under the epidermis indicates satisfactory injection.

Amount to be injected.—Since oxygen is not toxic in any quantity, 5 to 6 litres may be injected without any difficulty.

In bad cases of asphyxia 500 c.c. is quite suitable. Subcutaneous emphysema may appear and is of no consequence.

CLASS B: Expectorants

Expectorants are drugs which increase bronchial secretion and help its expulsion. To appreciate this action it is necessary to understand the natural mechanisms for protecting the air passages. They are *motor* and *secretory*. The motor mechanism consists of (1) propulsive movement of the cilia which line the mucous membrane; (2) reflex expulsive mechanism of cough; and (3) peristaltic movements of the muscles of the smaller bronchi. The secretory mechanism keeps the bronchial surface moist and dilutes irritating substances. The mucous membrane therefore is supplied with a large number of glands. Both these functions, *viz.* the motor and secretory, are regulated by the vagus and sympathetic nerves. The afferent fibres of the vagus transmit impulses from the mucous membrane, while the efferent fibres supply the muscles and the secretory glands. The muscles are also supplied by the efferent fibres of the sympathetic. Both these sets of fibres converge upon a hypothetical *cough centre* which is related to the respiratory and vomiting centres.

Gunn has classified expectorants as follows:—*

1. *Reflex expectorants*.—Most of the expectorants belong to this class. They act by stimulating the sensory ends of the vagus in the stomach and when given in large doses act as emetics. To this class belong tartar emetic, ipecacuanha, senega, quillaia, squill, ammonia, carbonate of ammonia, alkalies, apomorphine and camphor.

Similarly stimulation of the sensory endings of the vagus in the bronchial mucous membrane also increases bronchial secretion. Volatile oils, oleo-resins, balsams, etc., act in this way. These produce mild irritation during excretion through the bronchial mucous membrane.

2. *Central expectorants*.—To this class belongs apomorphine, which increases the secretion by stimulating the centre. Ipecacuanha and tartar emetic may have a central effect. The centre for bronchial secretion being closely associated with the vomiting centre in the medulla, emetics in small doses act as expectorants.

3. *Those acting by stimulating the secretory nerve endings*.—Pilocarpine belongs to this group and acts by stimulating the parasympathetic endings.

4. *Those acting by stimulating the bronchial glands*.—Iodides increase secretion of the bronchial mucus by acting on the secreting cells during excretion. It was formerly believed that most expectorants, specially ammonium chloride and alkalies, acted by increasing the secretion of bronchial glands.

Administration of expectorants depends upon a proper appreciation of the condition of the patient, the type of cough, the character of the sputum and the correlation with the stages and clinical features of the causative disease. Expectorants may be therapeutically classified as follows:—

- * I *Stimulant expectorants*.—These are excreted by the bronchial mucous membrane which is mildly irritated resulting in increased bronchial secretion. This mild irritation is supposed to help repair. The drugs belonging to this group are mostly volatile oils and aromatics, and Sollmann calls these, *aromatic expectorants*. They are volatile oils, terebene, balsam of Peru and tolu, camphor, benzoates, creosote, guaiacol, etc.

- II. *Sedative expectorants*.—These are specially selected to check excessive or harassing cough. They belong to different classes and act in the following ways:—

* *British Medical Journal*, Vol. II, 1927

(1) By soothing acute inflammation or irritation by increasing the secretion of protective mucus in the bronchioles without directly irritating the mucous membrane. They are chiefly the *reflex expectorants* (see page 308), also called *nauseant expectorants*. They are tartar emetic, ipecacuanha, apomorphine, etc. *Demulcents*, like liquorice, acacia, glycerin, althea, etc., also act as sedatives.

(2) By liquefying thick tenacious mucus. To this class belongs the salines like potassium iodide, chloride and carbonate of ammonium, bicarbonates of potassium and sodium, etc., these are also called *saline expectorants*.

(3) By controlling excessive cough reflex. They are mostly preparations of belladonna, and opium or its alkaloids, *e.g.* tinct. opii camph., pulv. ipecac. et opii, codeine, dionin, etc. Since they reduce the secretion they should not be used when the secretion is profuse. These are also known as *anodyne expectorants*. Syr. prun. serot. also acts as a sedative expectorant.

III. *Antispasmodic expectorants*.—Although these do not act as true expectorants inasmuch as they do not increase the secretion of mucus or make it less viscid, they help expulsion of mucus by relaxing the bronchial muscles, and are of great value in bronchial asthma, and chronic bronchitis. They are belladonna, lobelia, nitrites, grindelia, ephedrine and adrenaline.

IPECACUANHA

Ipecacuanha. (Ipecac.)

Syn.—Ipecacuanhæ Radix; Hippo.

Source.—The dried root of *Cephaelis Ipecacuanha*. Contains not less than 2 p.c. of the total alkaloids, calculated as *emetine*.

Characters.—Tortuous pieces, up to 15 cm. long, and 6 mm. thick, colour dark brick-red or brown, closely annulated. Fractured surface exhibits a wide, greyish bark and a dense central portion. Odour, slight. Taste, bitter.

Composition.—Three alkaloids from 2 to 3 p.c., of this (1) *Emetine* 72 p.c. (2) *Cephaeline* 26 p.c. (3) A third alkaloid *Psychotrine* 2 p.c. (4) Methylpsychotrine and emetamine, present in small proportion. (5) Ipecacuanhic or cephaelic acid. (6) Starch, volatile oil, gum, etc.

OFFICIAL PREPARATIONS

1. *Extractum Ipecacuanhæ Liquidum*.—Contains 2 p.c. w/v of the alkaloid emetine, or $\frac{1}{5}$ gr in 2 ms. B.P. Dose— $\frac{1}{2}$ to 2 ms. or 0.03 to 0.12 mil, 10 to 30 ms. or 0.6 to 2 mils as emetic.

2. *Tinctura Ipecacuanhæ*.—Contains 0.1 p.c. w/v emetine, or $\frac{1}{17}$ gr. in 30 ms. B.P. Dose—10 to 30 ms. or 0.6 to 2 mils; $\frac{1}{2}$ to 1 oz. or 15 to 30 mils as emetic.

N.B. The tincture should be supplied when Vinum is ordered.

IPECACUANHA PULVERATA

Powdered Ipecacuanha. (Ipecac. Pulverat.)

Syn.—Pulvis Ipecacuanhæ.

Source.—Ipecacuanha root reduced to a fine powder, and adjusted if necessary, by the addition of powdered lactose, to contain 2 p.c. of the total alkaloids, calculated as *emetine*. Contains $\frac{1}{15}$ gr. of emetine in 2 grs.

B.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.; 15 to 30 grs. or 1 to 2 grm. as emetic.

OFFICIAL PREPARATIONS

1. *Pulvis Ipecacuanhæ et Opii*. Syn.—*Pulvis Ipecacuanhæ Co., Dover's Powder*.—Contains $\frac{1}{16}$ gr. morphine in 10 grs. B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

2. *Trochiscus Morphinæ et Ipecacuanhæ*.—Contains $\frac{1}{2}$ gr. of morphine hydrochloride and $\frac{1}{10}$ gr. of ipecacuanha in each.

EMETINÆ Y OC LO I U

Emetine Hydrochloride. (Emet. Hydrochlor.)

Source—The hydrochloride of an alkaloid, emetine, obtained from ipecacuanha root or prepared by the methylation of cephæline.

Characters—Colourless, crystalline powder; odourless; taste, bitter. Soluble in water, and in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.03 to 0.06 grm. by injection.

OFFICIAL PREPARATION

1. *Emetinæ et Bismuthi Iodidum*.—A complex iodide of emetine and of bismuth. Contains 25 to 28 p.c. of emetine, and 18 to 21 p.c. of Bi. A reddish-orange powder. Odourless; taste, bitter, acrid. Insoluble in water. **B.P. Dose**—1 to 3 grs. or 0.06 to 0.2 grm.

NON-OFFICIAL PREPARATIONS

1. *Syrupus Ipecacuanhæ*, U S P.—Fluid extract of Ipecacuanha 7, glycerin 10, syrup qs. to 100. **Dose**, U S P.—Expectorant, 12 ms. or 0.75 c.c.; emetic, 4 dis. or 15 c.c.

2. *Emetine Periodide*, ($C_{20}H_{40}N_2O_4I_2$)—Introduced as a substitute for emetine-bismuth-iodide. Contains 33.7 p.c. of emetine. Can be given by the mouth without any local effect. Completely insoluble in weak acids. Dissolved and split up by weak alkalis. Supposed to be most effective and least toxic of all emetine preparations. Useful in refractory cases of amoebic dysentery. **Dose**—2 grs. thrice daily after food for 15 days.

3. *Gavano*.—It is *mono-methyl ester of cephæline* in combination with an organic acid. Supposed to be of value in *chronic intestinal amœbiasis*. It can be taken by the mouth without nausea and vomiting, or any toxic effect on the heart. It is however not so effective in chronic cases as emetine bismuth iodide or kurchi-bismuth iodide, but it is useful in acute cases specially where the liver is involved. **Dose**.—One tablet thrice daily for six days.

PHARMACOLOGY

Externally.—Powdered ipecacuanha acts as an irritant, rubefacient and pustulant on the unbroken skin. Emetine in 1 in 100,000 solution was thought to be destructive to amœbæ both pathogenic and non-pathogenic. But more recent observations have shown that a solution of 1 in 5000 kills amœbæ in broth cultures, while stronger solutions (1 in 100 to 1000) are required to destroy these organisms in bits of mucus freshly obtained from the intestine. It kills anthrax bacilli.

Internally **Alimentary canal and liver**.—Ipecacuanha has an unpleasant bitter taste and excites the flow of saliva. In small doses ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) it increases the secretion of the gastric juice by stimulating the local circulation, and is therefore stomachic and tonic. In larger doses, 15 to 30 grs., it produces vomiting by its direct influence on the peripheral ends of the vagus, hence it is a **direct emetic**. The vomiting is slow but certain and is unaccompanied by much nausea or prostration. It also acts as an emetic by acting on the centre in the medulla, but this effect is not observed in the ordinary methods of administration. In drop doses ipecac-

uanha tincture acts as an antiemetic in certain conditions. Emetine is a local irritant, and $\frac{1}{2}$ gr. given by the mouth causes nausea and vomiting followed by looseness and griping. The prolonged use of emetine induces diarrhœa, known as emetine diarrhœa. Given intravenously it is partly excreted by the intestinal mucosa, at the same time improves the tone and movement of the gut

The liver is directly stimulated by the alkaloids of ipecacuanha and there is a plentiful secretion of bile

Heart and circulation — Emetine depresses the excitability and conductivity of the heart and slows the beat which

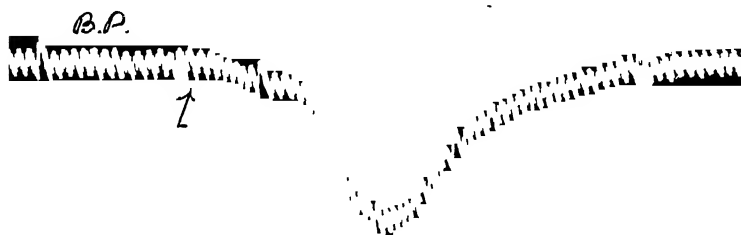


Fig 15.—Dog Showing effect of Emetine on Blood-pressure At the point of arrow 1 c.c. of a 0.1 pc solution was introduced into the femoral vein. Note the fall of pressure due to depression of the heart and dilatation of the vessels

is not influenced by cutting the vagi or administration of atropine. The heart becomes irregular, auricular and ventricular dissociation may be induced and death may occur from auricular and ventricular fibrillation, the heart stopping in diastole (Chopra and Ghosh). In toxic doses the heart becomes progressively slow and weak with fall of blood-pressure followed by collapse. These effects are more marked when emetine is given intravenously. Tachycardia with giddiness may follow therapeutic doses of emetine. It is toxic to the capillary endothelium producing petechial hæmorrhage. In toxic doses the vessels dilate, while non-toxic doses given intravenously lower carotid pressure but increase pulmonary pressure.

Nervous system.—In frog it produces a slowly advancing central paralysis. In man there is a general depression producing weakness and lethargy, or there may be neuritis. In toxic doses there is degeneration of the anterior horn cells.

Respiratory tract.—It is an expectorant acting reflexly through the stomach. During elimination it also stimulates the bronchial mucous membrane and renders the secretion more fluid. Toxic doses of emetine have a tendency to

pulmonary congestion, or to hæmorrhagic pneumonic consolidation.

Skin.—Moderate doses ($\frac{1}{2}$ to 1 gr) stimulate the skin and produce diaphoresis, which action is increased by the combination with opium (Dover's powder).

Uterus.—It has been suggested that emetine should be avoided during pregnancy as it may cause abortion. Experi-

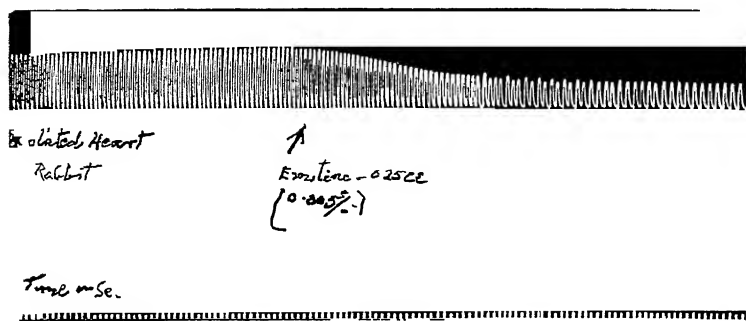


Fig. 16—Tracing of the Movements of the Isolated Rabbit's Heart during Perfusion. At the point of arrow 0.25 c c. of 0.005 p.c. solution of emetine hydrochloride was introduced into the fluid. Note weakening and slowing of the heart. The force of systole getting weaker and weaker. Upstroke, systole.

ments with strips of rabbit's uterus have shown that emetine in dilutions of 1 in 150,000 to 1 in 100,000, the concentration attained after a dose of one grain in man, assuming that the whole of the alkaloid is in solution, has very little effect on the uterus. Since emetine does not produce contraction of the uterus it cannot be a factor in causing abortion, which is probably due to bacterial toxin and not to emetine.*

Acute toxic action.—Emetine is cumulative. Severe diarrhoea, abdominal pain, tenesmus and toxic delirium have been reported from $\frac{1}{2}$ gr doses used for four days. Spehl and Collard noticed flaccid paralysis of the muscles of the neck with dysphagia and difficulty of mastication and speech, œdema of the face, and rapid, weak heart from 22 grs. given in 18 days. Acute renal insufficiency, general œdema, hæmoptysis, flaccid paralysis, peripheral neuritis, delirium, coma, and failure of the heart are the toxic symptoms.

THERAPEUTICS

Internally. Alimentary canal.—As a stomachic tonic, powdered ipecacuanha ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) is used with other stomachics and bitters in atonic dyspepsia. Ipecacuanha tincture in 1 m. doses, every quarter to half hour, checks the vomiting of pregnancy and gastric irritability during febrile attacks and other diseases. In cases where it fails

* R. N. Chopra and B. N. Ghosh, *Indian Medical Gazette*, 1922.

it may be given with $\frac{1}{4}$ minim of dilute hydrocyanic acid with good results. Ipecacuanha is not a suitable emetic in poisoning as its action is tardy, but it is exceedingly efficacious in croup and bronchitis of children, not only by mechanically expelling the mucus, but by its influence on the respiratory mucous membrane. 60 to 120 ms. of the tincture must be given every 1 or 2 hours until the child vomits. With some it merely acts as a purgative. It makes an excellent emetic in bilious attacks and in the early stage of fevers.

Powdered ipecacuanha in 20, 30 or even 60 or 90 grs. doses was formerly used in the treatment of acute amœbic dysentery, but it had the drawback of producing nausea and vomiting. To prevent its being rejected it was administered in keratin-coated pills, or an opium draught, or a hypodermic injection of morphine, was given an hour before the administration of the drug. Both in acute hepatitis and in amœbic dysentery the treatment by ipecacuanha *per os* has been replaced by the daily subcutaneous injection of emetine hydrochloride in doses varying from $\frac{1}{4}$ gr. to 1 gr., the most effective dose for adults being 1 gr. In effecting a cure co-operation of the host is necessary, and it is possible that the reticulo-endothelial system plays an important part (see page 66). Emetine treatment should be accompanied by the administration of bismuth carbonate as its effects are better if the reaction of the gut is rendered alkaline. In both these diseases pain, tenderness and fever in hepatitis, and blood, mucus and tenesmus in dysentery, rapidly disappear. Being, however, of no value in bacillary dysentery it may be of value for purposes of differential diagnosis. It should be remembered that emetine is a cumulative and highly poisonous drug, and its prolonged use is followed by diarrhœa, lassitude, general weakness, paralysis of muscles, and weakness of the heart. There may be peripheral neuritis with weakness or even paralysis of extremities, but this is very rare. The administration of the remedy should be stopped on the appearance of any of the toxic symptoms. In fact, not more than nine injections should be given in one course.

In chronic forms with encysted amœbæ and in carriers, emetine-bismuth-iodide in keratin-coated pills, tablets, or in cachets, should be given by the mouth at bedtime. The object being to enable the drug to pass through the stomach unchanged and to liberate emetine in the intestine where it will unfold its action directly on the entamœba, while emetine given hypodermically does not reach the part in sufficient concentration to be active. The only drawback is that it causes intense nausea and vomiting, and that hard tablets coated with keratin often pass out unchanged. The results are however disappointing; while some cases respond to this drug others require the use of either acetarsone (sto-

varsol), carbarsone or chiniofonum. In subacute and chronic cases and diarrhœa, Dover's powder acts well. In pyorrhœa alveolaris emetine destroys the *Entamoeba buccalis*, but since the amœba is not the cause of pyorrhœa it fails to cure.

It is also used in the treatment of **Bilharziasis** with success, though not so efficacious as antimony. Since amœbic dysentery may also be a common complication of this disease, its use serves the double purpose, and it can be used in cases with advanced renal and hepatic disease or in those intolerant to antimony. It may be used *intravenously*, but in complicated cases should be used *intramuscularly*. The usual dose for intravenous use is 0.06 grm. the 1st day, 0.09 grm. 2nd day, and then 0.1 grm. on the 3rd, 5th, 7th, 9th and 10th days with a total of 0.65 to 0.75 grm. It has also been recommended in dracontiasis.

Ipecacuanha is a most effective remedy for catarrhal jaundice and torpidity of the liver when given alone or combined with other cholagogues, and is a favourite constituent of aperient and cathartic pills.

Respiratory passages.—As an expectorant ipecacuanha in the form of tincture, liquid extract, lozenge or syrup, is daily used in different inflammatory conditions of the respiratory passages, *e.g.* in cold, catarrh, acute and chronic bronchitis, and broncho-pneumonia. In these conditions it is used in smaller doses so as not to induce emesis. Ipecacuanha is also recommended in hay asthma and whooping cough. In acute pneumonia large doses have been given with success.

Emetine has been used in hæmoptysis, but clinical results are not very encouraging unless accompanied with a high blood-pressure; on the other hand there is risk of pulmonary congestion.

A P O M O R P H I N E H Y D R O C H L O R I D E

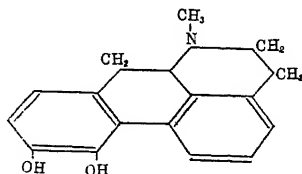
(Apomorph Hydrochlor)

Apomorphine Hydrochloride. $C_{17}H_{17}NO_2 \cdot HCl, \frac{1}{2}H_2O$

Source.—The hydrochloride of an alkaloid apomorphine obtained from morphine by the abstraction of elements of a molecule of water.

Characters.—Minute, glistening crystals; colourless or greyish-white, turning greenish on exposure to light and air; faintly acid.

Solubility.—1 in 50 of water.



B.P. Dose.— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.001 to 0.002 grm. as expectorant; $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.002 to 0.008 grm. as emetic or hypnotic (subcutaneously).

NON-OFFICIAL PREPARATION

1 Syrupus Apomorphinae, B.P.C.—Apomorphine Hydrochloride 0.05, Acid Hydrochloric Dil. 0.25, Alcohol (90 p.c.) 4.5, Aqua 4.5, Syrup to 100. *Dose*— $\frac{1}{2}$ to 1 dr. or 2 to 4 mils

• PHARMACOLOGY

Externally.—A 1 p.c. solution dropped into the eye causes anaesthesia but it may cause local pain and may induce vomiting from absorption.

Internally. Stomach.—Apomorphine is a reliable emetic acting directly on the vomiting centre. It acts within 10 to 15 minutes with the usual attendant symptoms of vomiting, *viz.* salivation, increased secretion from the nose, throat and bronchial passages, and cold perspiration. These effects, however, are not due to any direct action of the drug on the stomach. The central effect was proved by Eggleston and Hatcher by injecting into animals from which the whole alimentary canal from the cardia to the anus, was removed but who showed typical retching, vomiting movements and expulsion of mucus from the mouth and oesophagus. On the other hand direct application of the drug to the oesophagus or pharynx did not produce vomiting although emesis occurred in animals if the drug was applied directly to the floor of the fourth ventricle in the region of the vomiting centre. It does not irritate the stomach, and produces emesis when other emetics given by the mouth fail. $\frac{1}{3}$ gr. given per rectum also induces vomiting.

Heart and circulation.—In medicinal doses it has no action on the heart and blood-vessels, beyond a slight depression from the effect of vomiting, but in large doses it increases the frequency of the pulse, probably by stimulating the accelerator nerves.

Respiratory tract.—Unlike morphine, which in large doses depresses the respiratory centre, apomorphine in large doses stimulates the centre. Like all emetics, when given in small doses, apomorphine increases the secretion of bronchial mucus and makes it less viscid. This hypersecretion is also due to its direct influence on the cough centre. Very large doses paralyse the central nervous system, death takes place from respiratory failure although the heart continues to beat for some time.

Nervous system.—In large doses apomorphine produces excitement in animals which do not vomit. The respiration becomes quickened, but remains regular. In toxic doses there is ataxia and violent and irregular convulsions.

THERAPEUTICS

Internally—As a prompt and certain emetic, apomorphine is invaluable in poisoning, *i.e.* in narcotic poisoning, drunkenness, etc. For this purpose $\frac{1}{10}$ gr. hypodermically

acts within 1 to 2 minutes; although given by the mouth it may produce vomiting after absorption, but large doses are necessary. A plum-stone obstructing the œsophagus was removed by vomiting induced by apomorphine. As an expectorant, it is always given by the mouth. In the early stage of the inflammation of the larynx, trachea and bronchi, when the mucous membrane is dry or secretes a viscid tenacious mucus, apomorphine loosens the secretion and removes inflammation. In croup and acute bronchitis of children it is useful. In subacute or chronic bronchitis, broncho-pneumonia, chronic catarrh of large tubes, or bronchial irritation caused by the inhalation of jute, flax, cotton or other foreign particles, it is most useful if the secretion is scanty and tenacious. In whooping-cough it has been found serviceable combined with morphine or codeine. Sometimes it can be usefully combined with morphine in the form of a linctus with syrup of wild cherry, syrup of tar or of lemon.* It is valuable in persistent hiccough. One injection of $\frac{1}{10}$ gr. often gives permanent relief.

It is sometimes used in very small doses hypodermically as a sedative in insomnia without producing vomiting if the dose is not exceeded beyond $\frac{3}{32}$ gr. It has been used in alcoholic excitement and delirium tremens.

Caution.—It should be given with great caution to the feeble, the aged, and children, and to those subject to chronic diseases of the heart and lungs.

SENEGA

Senega. (Seneg.)

Source.—The dried root of *Polygala Senega*.

Characters.—Greyish or brownish-yellow, slender, from 5 to 20 cm. long, with a knotty crown bearing the bases of numerous slender aerial stems; frequently curved or contorted, sparingly branched, keeled, sometimes transversely wrinkled. Fracture, short. Odour, distinctive, taste, at first sweetish, afterwards acid.

Composition.—It contains two glycosidal saponins, viz. (1) *Senegin*, (2) *Polygalic acid*, which resemble, but are not identical with *quillaja-sapotoxin*, the active principle of *quillaja bark*.

B.P. Dose.—6 to 12 grs. or 0.4 to 0.8 grm.

OFFICIAL PREPARATIONS

1. *Extractum Senegæ Liquidum*.—B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.
2. *Tinctura Senegæ*.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
3. *Infusum Senegæ Concentratum*.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils. Diluted with seven times its volume of water becomes equivalent to fresh infusion

*R̄

Apomorph. hydrochlor. gr 1
Syr̄ prun seiot. oz $\frac{1}{2}$
Syr̄ picis liq oz $\frac{1}{2}$

R̄

Apomorph. hydrochlor gr $\frac{1}{6}$
Codein. phosph. gr $\frac{1}{2}$
Acid hydrocyan dil. ms. 8
Syr̄ prun seiot. ad oz 1

One teaspoonful three or four times a day

One teaspoonful as linctus

4. *Infusum Senegæ Recens.*—B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mils. Fresh infusion should be used within 12 hours of its preparation.

PHARMACOLOGY

The action of senega depends chiefly on the presence of senegin which resembles sapotoxin. These saponins form froth when shaken with water and emulsify oils and resinous substances. Sapotoxin is an irritant to the gastro-intestinal tract and causes nausea, salivation, vomiting and sometimes diarrhœa. Both quillaia and senega contain these saponins. They are mixtures of various, generally colloidal, substances of a glycosidal nature which produce much local irritation when used subcutaneously. They are not absorbed by the healthy epithelium of the alimentary tract and are decomposed by the alkalies and ferments into inert compounds. Introduced directly into the blood in large doses they cause convulsions and respiratory failure which may cause death. Small doses produce gastro-intestinal irritation with symptoms resembling dysentery. They are specially destructive to red blood cells and set free hæmoglobin into the serum. This effect is due to their affinity for cholesterolin, and if they are saturated with cholesterolin they lose this hæmolytic property.

When inhaled senega causes sneezing and cough. Taken by the mouth it acts as an expectorant, due chiefly to its nauseant effect. Senegin is excreted through the bronchial mucous membrane and during excretion increases the secretion.

It is eliminated by the skin and the kidneys, and while doing so stimulates their action moderately.

THERAPEUTICS

The chief use of senega is as an expectorant in acute and chronic bronchitis and in pneumonia in the stage of resolution. It is of value in bronchiectasis. The best effects are obtained when senega is combined with ammonium carbonate.

Very small doses of senega (3 ms. of tincture to $\frac{1}{2}$ oz.) emulsify fats and oils, and the tincture may be used with advantage in making castor oil emulsion.

QUILLAIA

Quillaia. (Quill.)

Syn.—Quillaia Cortex; Panama Bark; Soap Bark.

Source.—The dried inner part of the bark of *Quillaja Saponaria* and other species of *Quillaja*.

Characters.—Flat pieces, 3 to 10 mm. thick, vary considerably in length and width. Outer surface brownish-white, or reddish-brown; inner surface smooth, white or yellowish-white. Taste, astringent, acrid. Powder irritates nostrils.

Composition.—(1) *Quillaja-sapotoxin*, and (2) *Quillajic acid* toxic glycosides, closely allied to saponin.

B.P. Dose.—1 to 3 grs or 0.06 to 0.2 grm.

Enters into.—The preparation of Liq. Picis Carbonis and the

OFFICIAL PREPARATION

1. *Tinctura Quillaia*—1 in 20. B.P. Dose.—30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The powdered soap bark is very irritant to the nostrils, giving rise to a nasal discharge, sneezing, and sometimes cough, and its inhalation is therefore recommended in acute and chronic catarrhal rhinitis.

Internally.—Quillaia bark contains five times more *saponin* or *senegin* than *senega*, and is therefore a more powerful expectorant. It may be given in chronic bronchitis, and emphysema with deficient expectoration, but its use is contra-indicated in hæmoptysis, or ulceration of the throat and alimentary canal, on account of its irritant properties. Because it contains a large percentage of *saponin*, it is largely employed for emulsifying resins and oils.

CLASS C: Bronchial Antispasmodics

These drugs when used either as inhalation or by the mouth relieve respiratory spasm by relaxing the bronchial muscles. The bronchial muscles are supplied by the parasympathetic (*vagus*) which constricts, and sympathetic which dilates. Relaxation of the bronchial muscle is indicated in asthma. The spasm is relieved by atropine, hyoscyne, etc., which depress the vagal endings; by lobeline which depresses the vagus nerve-endings or the ganglia; by adrenaline and ephedrine which stimulate the sympathetic nerve-endings; by nitrites and papaverine, which depress the muscle. Narcotics cause relaxation of the muscle by depressing the centre. Morphine in small doses also causes relaxation of the bronchial muscles. Smoking of stramonium or datura cigarettes, or inhalation of smoke of nitre papers will often give temporary relief. Unfortunately atropine though relaxes the bronchial muscles and thus relieves spasm has the drawback of diminishing bronchial secretion, which the sympathetic stimulants like adrenaline do not

The Bronchial Antispasmodics are :

Lobelia, *Adrenaline* (see page 292), *Ephedrine* (see page 295), *Atropine* (see page 243), *Nitrites* (see page 299), *Grindelia*.

L ELIA

Lobelia. (Lobel.)

Source.—The dried aerial parts of *Lobelia inflata*.

Characters.—Stems, rounded, channelled, furnished with narrow wings; purplish hairy, scarred. Leaves irregularly toothed and hairy. Capsules, inflated, two-celled containing brown seeds. Odour irritating. Taste, at first slight, after chewing, burning and acrid.

Composition.—It contains (1) *Lobeline*, an oily, volatile alkaloid, crystallises in broad colourless needles. (2) *Lobelic acid*.

B.P. Dose.—1 to 3 grs or 0.06 to 0.2 grm.

OFFICIAL PREPARATION

1. *Tinctura Lobeliae* *Ætherea*.—1 in 5. B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATION

1. *Lobeline Hydrochloride*.—The hydrochloride of the alkaloid derived from *Lobelia*. A white crystalline powder, soluble 1 in 50 of water, 1 in 10 of alcohol. Solution should not be heated. A powerful respiratory stimulant.

Dose — $\frac{1}{6}$ gr. or 10 mg. in 1 p. c. solution *intravenously*. *Max. Dose* — $\frac{1}{3}$ gr (0.02 grm.).

PHARMACOLOGY

The action of lobelia is due to the presence of the alkaloid lobeline which resembles nicotine in its effects. It first stimulates and then depresses the parasympathetic ganglia. An injection of lobeline therefore causes increased salivary and bronchial secretions, constriction of the bronchial muscle, increased intestinal movements, slowing of the heart and a rise of blood-pressure. These effects however pass off soon and are followed by opposite effects.

Gastro-intestinal canal.—Whether absorbed by the skin or the stomach, lobelia in large doses, produces gastro-intestinal irritation, causing vomiting, purging and great prostration. The vomiting is probably due to the primary stimulation of the vomiting centre.

Heart and circulation.—After the initial effect there is fall of blood-pressure. In cases of weak heart this effect may arrest it altogether. Usually however the heart returns to normal or there may be acceleration. These effects are due to the direct action on the muscle and on the vagus ganglia.

Respiration.—The bronchial muscles are relaxed and the effect is due to depression of the vagus endings or their ganglia. There may be an initial constriction from stimulation of the vagus ganglia. Lobeline lessens the CO₂ threshold and stimulates the respiratory centre causing considerable increase in pulmonary ventilation. It is therefore a respiratory stimulant.

Nervous system and muscles.—The convulsions are secondarily affected only by toxic doses, when coma, and sometimes convulsions, may occur. Besides its depressing effects on the cardiac, respiratory and vaso-motor centres, it lowers the activity of the motor centres of the cord, causing relaxation of muscles.

THERAPEUTICS

For its powerful bronchial antispasmodic action it is very often used in asthma. Large doses sometimes cause great depression. If there is more or less dyspnoea throughout 24 hours the patient must have 10 ms. thrice daily, besides a few extra doses during the paroxysm. Often speedier relief is obtained by combining it with bromides, and iodides.*

*R

Pot. brom	gr. 120
Pot. iod.	gr 120
Tinct lobel ether.	ms. 180
Tinct bellad.	ms. 60
Aqua chlorof	ad oz. 6

$\frac{1}{2}$ an ounce three or four times a day

It is used in spasmodic bronchitis and whooping-cough, relieving the paroxysmal dyspnoea and spasms.

Because it stimulates the respiratory centre, lobeline is used in pneumonia, poisoning by carbon monoxide and morphine, and in the asphyxia of the new born. It may also be used in any case of *sudden respiratory failure* and may be combined with cardiac stimulants. The usual dose is $\frac{1}{20}$ gr. (3 mg.) hypodermically. It may be used intravenously in cases of extreme urgency, but since it produces other side effects specially on the heart, it should be used with caution in patients with weak myocardium.

GRINDELIA (*Not official*)—Dried leaves and flowering tops of *Grindelia camporum*.

Composition—(1) *Amorphous resins* (20 p c.). (2) *Hentriacontane*, a crystalline phytosterol, various glycerides, *l*-dextrose, tannin, colouring matter and a trace of volatile oil.

NON-OFFICIAL PREPARATION

1 **Extractum Grindeliæ Liquidum**.—1 in 1 **Dose**.—10 to 20 ms. or 0.6 to 1.2 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—It locally stimulates the stomach and acts as a mild stomachic, and if continued too long it may cause gastric uneasiness.

After absorption it slows the heart and respiration, but its chief action is on the bronchial mucous membrane which it stimulates, and on the bronchial muscles, which it relaxes. It is therefore an expectorant and a bronchial antispasmodic. In large doses it powerfully depresses the respiratory and cardiac centres, dilates the pupil and causes sleep. The cutaneous sensibility and reflex movements are lessened, and there is incomplete paralysis of the limbs.

Its chief use is in asthma, 20 or 30 ms. of the liquid extract given every half or one hour relieve a paroxysm after two, three or four doses. The dried leaves mixed with nitre may be burnt and the fumes inhaled with advantage. It has been found serviceable in spasmodic bronchitis, emphysema, whooping-cough and other spasmodic respiratory troubles.

✓ CLASS D: Bronchial Sedatives

Persistent and ineffective cough, due to irritation of the throat or tenacious mucus, frequently gives trouble. Dry hacking cough is also common in phthisis. For relief of cough, belladonna, opium, heroin, codeine, dionin or wild cherry bark are indicated.

P UNUS SE OTINA

Wild Cherry Bark. (*Prun. Serot.*)

Syn.—*Pruni Virginianæ Cortex*.

Source.—The bark *Prunus serotina*, collected in autumn.

Characters.—Curved or channelled pieces or irregular fragments, about 3 mm. thick. Young bark smooth, reddish-brown marked with transversely elongated lenticels, and granular fracture. Old bark rough and nut-brown. Taste, astringent, aromatic and bitter. Odour after maceration with water, like bitter almonds.

Composition.—(1) *d*-mandelonitrile (*prunasin*) a glycoside; and (2) an enzyme *prunase*. These two bodies yield hydrocyanic acid,

benzaldehyde and dextrose in the presence of water. (3) A bitter principle, tannin, starch, resin, etc.

B.P. Dose.—15 to 30 grs or 1 to 2 grm.

OFFICIAL PREPARATION

1. *Syrupus Pruni Serotinæ*. *Syn.*—*Syrupus Pruni Virginianæ*.—
B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The syrup is a sedative, because of the presence of minute quantities of hydrocyanic acid. It is used as a sweetening and flavouring agent in cough mixtures, but it can also allay cough in tea-spoonful doses, on account of its sedative virtues.

CLASS E: Pulmonary Antiseptics

Since certain antiseptics are eliminated in the breath, it has been supposed that their internal administration should have a lethal effect on microbes in the lungs, chiefly the tubercle bacillus. For this purpose these drugs are largely used in the treatment of pulmonary tuberculosis, and other septic conditions of the lungs. It must be borne in mind that during elimination they are considerably diluted, and do not reach the lungs in sufficient concentration to exert any destroying effect on the micro-organisms when administered *per os*. Used as an inhalation, they may have some beneficial effect in conditions characterised by offensive odour of the breath.

The pulmonary antiseptics are:

Guaiacol, Creosote, Tar Preparations, Volatile Oils, mainly Oil of Siberian Fir, Oil of Eucalyptus, Terebene and Oil of Turpentine.

GUAIACOL

Guaiacol. $C_6H_4(OCH_3)OH$

Source.—May be prepared synthetically, or by the fractional distillation of wood-tar creosote.

Characters.—A colourless, oily, highly refractive liquid, or colourless crystals melting at 28°C. Odour, penetrating and smoky; taste, caustic. *Solubility.*—1 in 80 of water, freely in alcohol (90 p.c.), in ether, glycerin and in fixed oils. Sp. gr. 1.116 to 1.125.

B.P. Dose.—5 to 10 ms. or 0.3 to 0.6 mil.

C E S T U

Creosote. (Creosot.)

Syn.—Creasote.

Source—Obtained by the distillation of wood tar, and contains guaiacol, creosol and other phenols.

Characters.—A colourless or yellowish, highly refractive liquid; odour, penetrating and smoky; taste, acid. *Solubility.*—Slightly soluble in water, miscible with alcohol (90 p.c.), ether, chloroform, fixed and volatile oils. Sp. gr. not below 1.070.

B.P. Dose.—2 to 10 ms. or 0.12 to 0.6 mil.

NON-OFFICIAL PREPARATIONS

1. *Creosoti Carbonas*, U.S.P. *Syn.*—*Creosotal*.—A viscid, amber-coloured almost odourless and tasteless liquid, insoluble in water, containing carbonates of guaiacol and creosol. *Dose*, U.S.P.—15 grs or 1 gm.

2. Vapor Creosoti Co *Syn*—*Inhalatio Iodæ Co*—Creosote 2, Phenol 2, Tinct Iodine 1, Sp Ether 1, Sp Chloroform 2 Useful in tuberculosis, as inhalation from Yeo's inhaler

3. Guaiacolis Benzoeas *Syn*—*Benzosol*.—In colourless, almost odourless and tasteless crystals It is less nauseous *Dose*—4 to 12 grs. or 0·3 to 0·6 gm

4. Potassu Guaiacolsulphonas *Syn*—*Thiocol*.—White powder soluble in water. Combines the good effect of creosote and guaiacol without their disadvantages Especially useful for children. *Dose*— $7\frac{1}{2}$ to 15 grs or 0·5 to 1 gm

5. Guaiacol Camphorate. *Syn*—*Guaiacamphol*.—A combination of guaiacol and camphoric acid For *night sweats of phthisis* *Dose*.—5 to 10 grs or 0·3 to 0·6 gm

6. Guaiacol Cinnamate *Syn*—*Stynacol*.—Insoluble in water For *intestinal phthisis* *Dose*—5 to 15 grs. or 0·3 to 1 gm.

7. Guaiacol Carbonas *Syn*.—*Duotal*.—An inodorous, tasteless powder Insoluble in water. *Dose*—5 to 15 grs. or 0·3 to 1 gm.

PHARMACOLOGY OF GUAIACOL AND CREOSOTE

Externally—The action of creosote is very similar to that of carbolic acid, creosote being an antiseptic, disinfectant and deodorant, but as it is a complex product, its action is not always uniform, and cannot therefore be relied upon. Guaiacol is a local anæsthetic.

Internally. Gastro-intestinal tract—When applied to the mouth, both creosote and guaiacol produce smarting and salivation, and destroy the epithelium In the stomach they are supposed to depress the terminal filaments of the sensory nerves of the mucous membrane and to arrest putrefactive and fermentative processes by destroying low forms of vegetable life such as torulæ and sarcinæ without affecting the pepsin. Large doses cause nausea, vomiting, colic and diarrhœa, with frequent pulse and slow and laboured respiration, without producing any convulsion.

Guaiacol is an antipyretic and acts like the salicylates, and a powerful diaphoretic. 60 ms. mixed with olive oil or lanoline and rubbed over the skin causes profuse perspiration.

Secretions.—They are readily absorbed into the blood, and are eliminated by the bronchial mucous membrane and kidneys, which they stimulate, increasing the bronchial and urinary secretions, and if fetid removing their fœtor.

Micro-organisms—They act as poisons to microbes, especially to tubercle bacilli when locally brought into contact with them, as by inhalation.

THERAPEUTICS OF GUAIACOL AND CREOSOTE

Externally.—Creosote cannot be used as a general antiseptic on account of its indefinite composition. But as creosote vapour or creosote spray it is useful as inhalation in chronic bronchitis, phthisis, gangrene of the lungs, etc. A few drops of creosote or guaiacol rubbed on the pit of the stomach, the part being afterwards covered with cotton-wool, causes profuse diaphoresis, and will often bring down the temperature in cases of fever.

Internally. Gastro-intestinal tract.—A pellet of cotton-wool soaked in creosote or guaiacol relieves toothache when introduced into the cavity of the painful carious tooth. In small doses, 1 to 2 ms., they relieve nausea, vomiting and gastralgia. They also check fermentative dyspepsia and diarrhoea, when given with bismuth and alkalies. For internal use guaiacol is preferred.

Lungs.—Both creosote and guaiacol are considered specifics for phthisis, because of their supposed lethal effects on the tubercle bacilli. They must be commenced early and continued long and in increasing doses. Commencing with 5 to 10 ms. doses either may be increased up to 30 ms. Guaiacol carbonate and thiocol are better borne than creosote, and they may with advantage be combined with quinine. While some clinicians claim these remedies as valuable in relieving cough and expectoration and causing general improvement, others are equally sceptical and are of opinion that they are of little value. They often upset digestion when their use requires to be discontinued.

Prescribing hints.—Creosote or guaiacol may be given by mouth, in pilules, capsules, perles, emulsions or mixed with milk or cod-liver oil. Sometimes the mucus secretion of phthisis is wonderfully decreased by using the creosote spray. During hæmoptysis creosote treatment must be stopped. When combined with oxide of silver it forms an explosive compound unless previously mixed with some inert powder.

For inhalation, creosote may either be given alone or mixed with phenol upon a respirator, or it may be used in the form of the Vapor Creosote. The Brompton formula is: creosote 1, spirit of menthol (20 p.c.) 1, spirit of chloroform 1. The addition of spirit of chloroform makes it more sedative in its action.

CLASS F: Drugs used for X-ray examination of Lungs
and Bronchioles

Oleum Iodisatum

OLEU IO ISATU

Iodised Oil. (Ol. Iodisat.)

Syn.—Lipiodol, Iodipin

Source—Iodised oil is an iodine addition product of poppy-seed oil, and may be prepared by treating poppy-seed oil with hydriodic acid. Contains 39 to 41 p.c. of combined iodine.

Characters—A colourless or pale-yellow, clear, viscous, oily liquid, odour, slightly alliaceous, taste, bland and oily. On exposure to air and sunlight, it decomposes and develops a dark brown colour. Insoluble in water, soluble in ether, in chloroform, and in light petroleum.

ACTION AND USES

It has been used intramuscularly as a substitute for iodides in the treatment of asthma, syphilis and rheumatic

affections. But its chief use is to visualise bronchi and their ramifications, bronchial and pleural fistulæ, permeability of bronchial fields, localisation of pulmonary cavities, and spinal cord compression. 20 to 30 c.c. is injected into the trachea either through a canula introduced through the glottis or through a curved needle inserted through the cricothyroid membrane, after anæsthesiation with cocaine. As a rule most of the drug is thrown out with the expectoration. A portion may be absorbed and excreted through the urine and saliva. When injected into the cisterna magna or into the lumbar region it helps to localise spinal cord compression. It is non-toxic and produces no reaction when given subcutaneously or intramuscularly. A case of death has recently been recorded.

GROUP VIII

DRUGS ACTING ON THE GASTRO-INTESTINAL TRACT

Mouth.—Normally the mouth harbours a large number of bacteria, and although the majority of them are harmless saprophytes, under favourable conditions they are capable of developing pathogenic properties. Since many diseases arise from oral sepsis, the condition of the mouth is of great significance. Pyorrhœa alveolaris, infected tonsils and some forms of stomatitis have been known to produce diseases in some distant parts of the body. Oral sepsis is also a common cause of complication, through secondary infection, in diseases like typhoid, pneumonia, apoplexy, etc. A clean mouth therefore is of great importance in therapeutics. Unfortunately it is very difficult to keep the mouth sterile for more than a few minutes, although the use of disinfectants check the growth and further progress of the bacteria. The best means of keeping the mouth clean is by the use of dentifrices and antiseptic mouth washes so that food particles cannot lodge in between the teeth where they can undergo fermentation and decomposition. In case of septic condition of the mouth much can be done by cleaning the mouth with hydrogen peroxide; tincture of iodine, either as paint or as a gargle diluted with warm water, or by the systematic use of antiseptic tooth powder.

Treatment of pyorrhœa is unsatisfactory as it is very difficult to apply any disinfectant into the infected pockets. Attempts have been made to clip off the pockets and thus prevent accumulation of pus. Application of disinfectants by ionisation has been tried apparently with good result.

Dentifrices are preparations used for cleansing the teeth. They may be *antiseptic*, when they contain drugs like quinine, phenol, etc.; and *astringent*, when they contain preparations containing tannin, like kino, krameria, myrobalans, etc.

Antiseptic mouth washes contain boric acid, phenol, thymol, potassium chlorate, etc. A useful preparation is *Liquor Antisepticus* which is an imitation of the proprietary preparation *Listerine* (see thymol). Hydrogen peroxide with water or tincture of iodine with water may also be used (see Gargles, page 41).

Children often suffer from caries of the teeth, due either to acid-forming bacteria from decomposed food lodged between the teeth, or to deficiency of calcium in the system. Administration of cod-liver oil, or the use of food rich in vitamin D, with plenty of milk are indicated in cases of calcium deficiency. Normally whole milk supplies sufficient calcium and vitamin D. Butter, or liquor calciferolis may also be administered to supply vitamin D.

Salivary secretion.—The saliva performs, two definite functions, *viz* (1) initiates the process of digestion and aids the deglutition of food; and (2) washes out of the mouth any harmful substances. The salivary glands are supplied by (1) *sympathetic*, stimulation of which causes vaso-constriction and a scanty flow of viscid saliva; and (2) the *parasympathetic*, stimulation of which causes vaso-dilatation and a copious flow of saliva.

Normally the secretion of saliva is increased by (a) the *psychic reflex*, excited by the sight or smell of food; (b) the *chemical stimulation* of the nerves of taste in the mouth; and (c) *mechanical stimulation* induced by chewing; which also provokes a flow of saliva chiefly from the parotid. The amount of saliva also depends upon the condition of the water content of the blood, *e.g* after profuse perspiration and excessive purgation the secretion is diminished and the mouth becomes dry.

Drugs which increase the secretion of saliva are called **sialagogues**. They may act as follows:—

1. *By exciting the periphery of the afferent nerves.*—These are acids and acid salts, pungents, aromatics, volatile oils, bitters, alcohol, ether, chloroform. They act reflexly from the mouth. Nauseants, like ipecacuanha and tartar emetic, act by stimulating the sensory ends of the vagus in the stomach.

2. *By stimulating the parasympathetic endings.*—These are sometimes called **specific sialagogues**. They are pilocarpine, acetylcholine, physostigmine and muscarine.

3. *By stimulating the autonomic ganglia.*—Nicotine group first stimulate then depress

4. *By stimulating the sympathetic endings.*—Adrenaline and ephedrine.

Many drugs, such as mercury and potassium iodide, are excreted with the saliva and increase its secretion. This is counteracted by atropine

Drugs which decrease the secretion of saliva are called **antisialagogues**. They may act as follows:—

1. *By allaying irritation of the mouth*, as potassium chlorate, borax, astringent gargles, etc.

2. *By paralysing the parasympathetic endings.*—Atropine.

Opium and morphine also reduce salivary secretion by diminishing the excitability of the centres of sensory nerves.

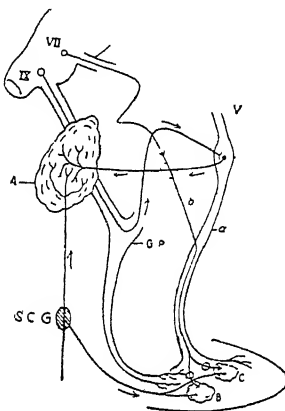


Fig 17—Innervation of the Salivary Glands A, parotid, B, submaxillary, C, sublingual glands s.c.g., superior cervical ganglion sending out sympathetic branches to the glands b, chorda tympani (parasympathetic) supplying the submaxillary and the sublingual glands, through the facial (After Mayer and Gottlieb).

DRUGS ACTING ON THE STOMACH

The stomach forms the reservoir for the reception of food which it reduces to a liquid or semi-liquid condition partly by digestion and partly mechanically. The solid food remains in the stomach for several hours, and during this period the musculature contracts in such a way that the more liquid portions as they are formed are ejected at certain intervals through the pylorus into the duodenum. Except at definite intervals when the pyloric sphincter relaxes, the

food is entirely shut off from the rest of the alimentary canal by the tonic contraction of both the pyloric and cardiac sphincters. The pyloric end protects the small intestine by preventing the passage of unassimilable material. This opening is under the control of reflex action, and opens only when the food material has reached a certain stage of digestion. It also prevents concentrated solutions from entering the small intestine without being suitably diluted.

Two sets of nerves control the movements of the stomach, *viz.* the *vagus* or *augmentor*, stimulation of which causes contraction, and the *splanchnics* or *inhibitor*, stimulation of which causes relaxation of the stomach and arrest of its movements, except the pyloric sphincter to which the fibres are motor. It is essentially an autonomic organ, gastric digestion may continue both as regards secretion and movements even after section of all the extrinsic nerves.

The gastric juice performs the following functions :—*

1. *Peptic digestion*.—This is helped by the secretion of pepsin and hydrochloric acid; and the most obvious function of the acid is to activate the pepsin to help the digestion of protein. This function however is not very important since the digestion of meat by the tryptic ferment remains unimpaired in the absence of hydrochloric acid.

2. *Antiseptic action*.—This is more important, as an acid secretion in the stomach kills many organisms, notably *streptococci*, which may be swallowed with food or carried from the mouth with saliva and other mucous secretions from the nose and pharynx. Moreover the dysentery, typhoid and cholera organisms are more or less killed by the gastric juice. Increased alkalinity of the contents of the small intestine, which results from the absence of hydrochloric acid in the stomach, favours the invasion of the duodenum, which is normally acid, with *B. coli* from the colon. The absence of hydrochloric acid therefore will favour infection of the small intestine with *streptococci* from above and with *B. coli* from below. These changes combined with the mechanical irritation of the mucous membrane with insufficiently broken down food will eventually lead to chronic enteritis.

3. *Hæmopoiesis*.—(a) *Iron absorption*.—Normally the food contains sufficient iron for the maintenance of the normal percentage of hæmoglobin in the blood. In case of achlorhydria there may be deficiency of food and consequently of food iron, or if there be any loss of blood, the amount of iron absorbed from food may not be sufficient to maintain iron equilibrium, and microcytic anæmia may result. But how far this is due to failure of acid in converting the food iron into more assimilable form, or the inability of the intestine to absorb iron owing to unhealthy condition, is not settled.

- (b) *Production of hæmopoietin*.—Castle has pointed out that the gastric juice contains a substance (intrinsic factor) which acts on the protein of the food (extrinsic factor) to produce a blood maturing principle essential for the maturation of the red blood corpuscles by the bone marrow, and its absence leads to Addisonian (pernicious) anæmia. This intrinsic factor which is of the nature of an enzyme has been named by Wilkinson as *hæmopoietin*.

4. *Production of Neuropoietin*.—It has recently been shown that the gastric juice also forms another substance allied to hæmopoietin which is essential for the normal nutrition of the central nervous system. It is also of the nature of an enzyme and its absence from the gastric juice leads to the degeneration of the posterior or the lateral columns of the spinal cord.

Gastric secretion is controlled by *vagus* which contains the secretory fibres. Stimulation of the peripheral end of the cut *vagus* is followed by secretion of the gastric juice. Pawlow and his followers have shown that the stomach of a hungry dog will secrete gastric

*Huist, *British Medical Journal*, Oct 13, 1934.

juice if he saw or smelled food, though there was no food in the stomach, and this was possible as long as the vagi were intact. It is evident that sensation of taste, odour, etc., reflexly stimulates the secretory fibres of the vagus, and the secretion so induced is termed "*psychic or appetite secretion*." This secretion initiates gastric digestion which is supplemented by further secretion arising in the stomach itself. It has therefore been suggested that this supplemental secretion is due to some chemical or hormonal stimulus. In fact Edkins* has shown that extracts of pyloric mucous membrane when injected into the blood cause an increased secretion of gastric juice. This has been attributed to the formation of *secretagogues* produced by some food and which acting on the pyloric mucous membrane form *gastrin* or *gastric secretin*, which being carried through the blood, acts as a chemical stimulus to the glands. Some foods, chiefly meat extracts, soup, etc., provoke the formation of this chemical stimulus, while white of egg, bread, and isotonic salt solution produce no such action.

1. **Drugs which increase the secretion of gastric juice are called stomachics.**—They act by various means, viz. (1) *reflexly by stimulating the nerves of the mouth*, so-called *psychic secretion*. Substances which stimulate the gustatory endings of the mouth in an agreeable manner and which excite sensation of appetite, increase the secretion of gastric juice. To this class belong good food, condiments and wine. Bitters and aromatics before meals stimulate psychic secretion reflexly through the nerves of taste; (2) *by stimulating secretory fibres of the vagus*, pilocarpine and muscarine; (3) *direct stimulation of the fundus*. Pawlow has shown that alcohol in concentration of above 5 p.c. increases gastric secretion by stimulating the mucosa of the fundus; (4) *stimulation of the pylorus*, certain meat extracts, fatty acids, soups, etc., act as chemical stimulus, probably through hormonal action; (5) *alkalies*, when given before meals increase the quantity of gastric juice.

Subcutaneous injection of histamine acid phosphate (1 mg) has been shown to increase gastric secretion, this it does in doses which have no effect on blood-pressure. It has been suggested that *gastrin*, and possibly also *secretin*, are probably histamine or a closely related derivative. How it acts is not known. 0.5 to 1 mg. is used intramuscularly to differentiate true from pseudo achylia and also to test the secretory response of the stomach in gastric troubles.

2. **Drugs which decrease the secretion of gastric juice.**—Increased secretion of gastric juice or hyperchlorhydria may occur and requires treatment. The secretion is diminished by (1) *Astringents*, e.g. salts of metals, opium, and substances containing tannin; these reduce vascularity and act as astringents; (2) *atropine*, which paralyses the vagus endings; (3) *fixed oils and fats*; (4) *alkalies*, these are largely used in certain forms of dyspepsia to neutralise excessive acidity due to lactic and fatty acids; the gastric juice is at first diminished but after recuperation the glands secrete more acid.

Just as peripheral stimulation increases psychic secretion, so also excitement, violent emotion and anxiety inhibit this secretion. Iced water will also diminish the secretion. Drinking iced water during or just before meals is therefore not desirable for proper digestion.

3. **Drugs modifying the composition of gastric juice.**—Gastric juice may be deficient, or may be excessive (hyperchlorhydria). Deficiency may be due to disease of the stomach, when less acid is secreted; or may be due to excessive accumulation of mucus, as happens in chronic gastritis. It is often absent or deficient in febrile conditions and many other diseases. Hyperchlorhydria is common in patients suffering from gastric ulcer. Excessive secretion is treated by alkalies. Of this magnesium oxide is best as it does not form carbonic acid which itself excites formation of gastric secre-

* *Journal of Physiology*, 1906.

tion. Calcium and magnesium carbonates come next and are stronger than bicarbonates of sodium and potassium. Bismuth carbonate is least powerful.

To help digestion hydrochloric acid dilute is given alone or with pepsin. The deficiency of ferment is treated with such drugs as pepsin, pancreatin, papain and taka diastase.

4. **Drugs modifying gastric movements.**—Excessive movements of the stomach demand the use of drugs which have a soothing effect on the mucous membrane, or which will act through the motor mechanism. *Gastric sedatives* are drugs which soothe the mucous membrane of the stomach. They are cocaine, chlorbutol, or those which relieve vomiting (see antiemetics, page 336). Atropine and adrenaline reduce excessive movements, the former by depressing the vagus, the latter by stimulating the sympathetic. Opium diminishes gastric movements by acting on the muscle and causes contraction of the pyloric sphincter. Insoluble salts of bismuth, magnesium and calcium form protective coating and reduce gastric movements, while cocaine, hydrocyanic acid dilute, chlorbutol and chloroform depress the sensory endings and reduce reflex movements of the stomach.

The effect of acids and alkalis on gastric movements is of some practical value. The presence of free acid in the stomach causes closure of cardiac orifice, increases pyloric peristalsis and opens the pyloric sphincter and allows the gastric contents to enter the duodenum. The presence of free acid in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. It will thus be seen that the control of the pyloric sphincter depends more upon the duodenum than on the stomach. Irritant solutions however cause closure of the pylorus, as happens when emetics are used, or when there are irritating food materials, when the stomach itself will reject by emesis, whereby the cardiac sphincter opens and the pyloric sphincter remains closed. Alkalies as a rule retard the emptying of the stomach, but the contents are emptied almost at the same rate when they are feebly alkaline or acid, or neutral.

5. **Drugs that help expulsion of gas, or carminatives.**—These act by (1) exciting regular peristaltic movements; (2) dilating either the cardiac or sometimes the pyloric sphincters; and (3) stimulating the nerves and muscles. The volatile oils are best in this respect. Aromatics and aromatic bitters, camphor, menthol, spirits, etc., are used to expel gas from the stomach.

CLASS A : Vegetable Bitters

The quality of bitterness is widely distributed throughout the vegetable kingdom, but many drugs, while possessing the bitter taste, have other and more important actions which overshadow the bitter quality. *e.g.* nux vomica on the nervous system, and quinine as antiperiodic. On the other hand, bitterness is the only quality of the drugs of this group and their therapeutic uses are linked with this property. Bitters in this sense form a class of the larger group of *stomachics*.

Bitters are divided into :—

- (a) *simple bitters*, like calumba, quassia, gentian, chirata; and
- (b) *aromatic bitters*, serpentary, aurantii cortex. The presence of volatile oil in this group materially adds to the stimulating effect.

CALUM A

Calumba. (Calumb.)

Syn.—Calumbæ Radix.

Source.—The dried transversely or obliquely cut slices of the root of *Jateorhiza palmata*.

Characters.—In irregular, flattish, circular or oval, centrally depressed pieces, 2 to 6 cm or more in diameter, 3 to 12 mm in thickness, yellowish. Cork, brownish, wrinkled, cortex, thick with radiating lines.

Composition—(1) *Columbin*, a colourless crystalline bitter principle (2) Three yellow crystalline alkaloids allied to berberine—*Columbamine*, *Palmitine* and *Jateorhizine*. (3) *Columbic acid* (4) *Starch*. (5) *Mucilage* No tannic acid

B.P. Dose—10 to 30 grs. or 0.6 to 2 grm

OFFICIAL PREPARATIONS

- 1 Infusum Calumbæ Concentratum—B.P. Dose—30 to 60 ms. or 2 to 4 mls
- 2 Infusum Calumbæ Recens—Fresh infusion should be used within 12 hours of its preparation B.P. Dose— $\frac{1}{2}$ to 1 oz or 15 to 30 mls
3. Tinctura Calumbæ—10 p.c B.P. Dose—30 to 60 ms or 2 to 4 mls.

QUASSIA

Quassia. (Quass.)

Syn—Quassia Lignum

Source—The wood of the trunk and branches of *Picræna excelsa*.

Characters—Logs of varying length, or in chips or raspings, yellowish white, tough, dense, but easily split. Inodorous Taste, intensely bitter.

Composition—(1) *Quassin*, a mixture of α -picrasmin and β -picrasmin, bitter principle No tannin

B.P. Dose—2 to 8 grs. or 0.12 to 0.5 grm

OFFICIAL PREPARATIONS

- 1 Infusum Quassia Concentratum—B.P. Dose—30 to 60 ms or 2 to 4 mls.
- 2 Infusum Quassia Recens—B.P. Dose— $\frac{1}{2}$ to 1 oz or 15 to 30 mls Should be used within 12 hours of its preparation
- 3 Tinctura Quassia—10 p.c B.P. Dose—30 to 60 ms. or 2 to 4 mls

GENTIANA

Gentian. (Gentian.)

Syn—Gentianæ Radix.

Source—The dried rhizome, and root of *Gentiana lutea*

Characters—In yellowish-brown, entire or longitudinally split wrinkled cylindrical pieces, seldom exceeding $2\frac{1}{2}$ cm thick, varying in length, encircled by leaf-scar and terminated by a leaf-bud Tough when moist, brittle when dried Fractured surface reddish yellow, central portion soft, not radiate Odour characteristic. Taste, first sweetish, then bitter Should not yield reactions with starch.

Composition—Contains (1) *Gentuin*, a glycoside, and (2) *Gentiamarin*. (3) *Gentianic acid* (4) A trisaccharide, *Gentianose*, pectin and oil.

Incompatibles—Iron and lead salts, silver nitrate.

B.P. Dose.—10 to 30 grs or 0.6 to 2 grm

OFFICIAL PREPARATIONS

- 1 Extractum Gentianæ.—B.P. Dose.—2 to 8 grs or 0.12 to 0.5 grm.
- 2 Infusum Gentianæ Compositum Concentratum—B.P. Dose—30 to 60 ms. or 2 to 4 mls.
- 3 Infusum Gentianæ Compositum Recens—B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.
- 4 Tinctura Gentianæ Composita—1 in 10 B.P. Dose.—30 to 60 ms. or 2 to 4 mls.

CHIRETA

Chiretta. (Not official)

Syn. I V—*Chireta*, Beng *Charayta*, Hind *Bhunimba*, Sans

Source—The dried plant, *Sacra Chirata*, collected when in flower.

330 PHARMACOLOGY AND THERAPEUTICS

Composition.—(1) *Cheratin*, an active amorphous bitter principle in combination with (2) *Ophelic Acid* No tannic acid

NON-OFFICIAL PREPARATIONS

1. *Infusum Chiratae* —1 in 20 ($\frac{1}{2}$ hour). *Dose* — $\frac{1}{2}$ to 1 oz or 15 to 30 mls
2. *Tinctura Chiratae* —*Dose* — $\frac{1}{2}$ to 1 dr or 2 to 4 mls.

SE PENTA IA

Serpentary. (Serpent.)

Syn —Serpentariae Rhizoma.

Source —The dried rhizome and roots of *Aristolochia reticulata*, known in commerce as Texan serpentary

Characters —Rhizome, tortuous, about 1 to 2 cm long and about 2 mm. thick, the upper surface bearing remains of aerial stems up to about 2 mm diameter; on the under surface numerous wily roots about 10 cm long and 0.2 to 1.2 mm thick. Odour odourless and camphoraceous, taste, strong, camphoraceous and bitter

Composition —A bitter principle apparently an alkaloid, *Aristolochine*, a volatile oil 1 p c. and tannin.

B. P. Dose — $\frac{3}{4}$ to 1 $\frac{1}{2}$ gr or 0.05 to 0.1 gm.

Enters into —Tinct Cinchonæ Co.

AU ANTHI CORTEX C NS

(Aurant. Cort. Rec.)

Fresh Bitter-Orange Peel

Syn I. V. —*Kamla nebur khosa*, Beng *Narengi ke bokla*, Hind

Source —The fresh outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus Aurantium*

Characters —Thin strips with but little of the white spongy part of the pericarp attached. Outer surface, red or deep orange-red and pitted. Epidermal cells, small and polygonal, parenchymatous tissue containing large oil glands and numerous crystals of calcium oxalate. Odour, fragrant, taste, aromatic and bitter

OFFICIAL PREPARATIONS

1. *Tinctura Aurantii* —1 in 4 B. P. *Dose* —30 to 60 ms. or 2 to 4 mls.
2. *Syrupus Aurantii* —1 in 8. B. P. *Dose* —30 to 120 ms or 2 to 8 mls

AU ANTHI CO TEX SICCATUS

(Aurant. Cort. Sic.)

Dried Bitter-Orange Peel

Source and Characters. —The dried outer pericarp of the ripe, or nearly ripe fruit of *Citrus Aurantium*.

Composition —(1) A volatile oil, 1 to 2 p c, which consists of a terpene, dextro-rotatory limonene (2) Three glycosides—hesperidin, iso-hesperidin, aurantiamarin, a bitter principle.

Enters into. —Inf Gent. Co Rec, Tinct Gent Co, Tinct Cinchon. Co

OFFICIAL PREPARATIONS

1. *Infusum Aurantii Concentratum* —B. P. *Dose* —30 to 60 ms. or 2 to 4 mls.
2. *Infusum Aurantii Recens* —B. P. *Dose* — $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

PHARMACOLOGY OF BITTERS

Internally. —Pure bitters stimulate the nerves of taste and reflexly increase the salivary and gastric secretions. Bitters have no action on the stomach, and introduced

directly into the stomach through a tube cause no increase of gastric secretion. It is the bitter taste that determines the action and by some reflex path they stimulate the activity of the gastric glands. As a consequence the appetite is sharpened and digestion is improved. The gastric ferments are not increased although the increase of gastric juice augments the flow of pancreatic secretion. Bitters are used as stomachics and appetisers. Their efficacy is increased by combining with aromatics and alcoholic preparations. Large doses produce opposite effects, *i.e.* diminish the secretion. If continued long they derange digestion by producing gastric catarrh.

In addition to the bitter property, aromatic bitters, because of the presence of volatile oils, act as carminatives and slightly increase the peristalsis.

Blood.—Most bitters, like volatile oils, produce leucocytosis.

THERAPEUTICS OF BITTERS

Bitters are daily used to promote appetite and digestion in cases where the stomach participates in the general enfeeblement of the functional activity caused by various diseases, overwork or starvation. They are specially valuable during the period of convalescence from acute diseases, but are contra-indicated in all diseases of the stomach that are accompanied by pain, vomiting, inflammation or ulceration, such as gastritis, gastrodynia, gastric ulcer, gastric cancer. An infusion may be injected into the rectum as an anthelmintic for thread-worms.

Prescribing hints.—Bitters should not be given in a concentrated form for a long time without interruption. Calumba is the least irritant of them all. Being free from tannin, calumba, quassia and chirata can be given with iron. They may be usefully combined with dilute hydrochloric or nitrohydrochloric acids; or if there is any irritability of the stomach, with alkalies and bismuth salts. They are generally used 20 to 30 minutes before food. Quassia being devoid of flavour is intensely bitter.

CLASS B: Digestive Ferments

Pepsin, Pancreatin, Papan, Malt, Taka Diastase

1. Proteolytic Ferments

PEPSINU

Pepsin. (Pepsin.)

Source.—A proteolytic enzyme of the gastric juice of animals. Obtained from the mucous membrane of the stomach of certain animals commonly employed for food.

Characters.—A colourless, or light buff-coloured, amorphous powder, or translucent scales; odour, faintly meaty; taste, slightly acid or saline. **Solubility.**—Moderately in water, insoluble in alcohol

332 PHARMACOLOGY AND THERAPEUTICS

(90 p.c.). Should dissolve 2,500 times its weight of coagulated egg albumen

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

1 *Liquor Pepticus*, B.P.C.—Stronger glycerin of pepsin, 125 mls, dilute hydrochloric acid, 35 mls, alcohol (90 p.c.) 100 mls, glycerin, 25 mls, distilled water q.s 1000 mls. *Dose*—1 to 2 dr or 4 to 8 mls.

2 *Mistura Bismuthi Composita cum Pepsino*, B.P.C.—1 dr contains concentrated solution of bismuth $\frac{1}{2}$ dr, pepsin 1 gr, tincture of nuxvomica $7\frac{1}{2}$ ms., dilute hydrocyanic acid 2 ms with chloroform, solution of bordeaux B and water. *Dose*.— $\frac{1}{2}$ to 1 dr or 2 to 4 mls.

3 *Mistura Bismuthi Composita cum Pepsino et Morphina*, B.P.C.—Contains $\frac{1}{10}$ gr. of morphine hydrochloride in 1 dr of *Mistura Bismuthi Composita cum Pepsino*. *Dose*.— $\frac{1}{2}$ to 1 dr. or 2 to 4 mls

4 *Glycerinum Pepsini*, B.P.C.—Pepsin 100 grm, hydrochloric acid 115 mls, glycerin 600 mls, water q.s to 1000 mls *Dose*—1 to 2 dr or 4 to 8 mls

5 *Peptone*.—A product of digestion of albuminoid substances. Occurs in nearly odourless, white or yellowish-brown amorphous powder, or in scales, with a cheesy taste. *Dose*—5 to 15 grs. or 0.3 to 1 grm by mouth, $\frac{1}{8}$ to $1\frac{1}{2}$ grs. or 0.01 to 0.1 grm by injection

6 *Seriparium*, B.P.C *Syn*—*Rennin*, *Rennet*.—An enzyme obtained from the glandular layer of the fourth or true digesting stomach of the calf having the property of coagulating or curdling milk Milk that has been previously boiled will not coagulate with rennet, as the calcium salts have been precipitated by boiling. The essence is largely used for the preparation of junket, rennet whey, etc. 1 to 2 drs will coagulate about a pint of milk

7 *Pulvis Pepsini Compositus*, B.P.C.—Pepsin, about 1 in 6, pancreatin, 1 in 10, and diastase 1 in 100 with lactic acid, hydrochloric acid and lactose *Dose*—10 to 30 grs or 0.6 to 2 grm.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Medicinal pepsin can convert outside the body in the presence of warmth, moisture and acidity, proteins (albumin, fibrin, etc) into peptones, and this action is taken advantage of in predigesting food; but the taste of the peptonised product becomes so unpalatable that it cannot be ordinarily prescribed.

Internally.—A similar process within the stomach, as seen outside, takes place when pepsin is given by the mouth. It is therefore a valuable agent in helping the digestion of those in whom the secretion of the gastric juice is deficient from:

- (1) Disease of the gastric follicles, as atrophy or dilatation.
- (2) Excessive secretion of mucus, as in chronic gastric catarrh, alcoholism.
- (3) Deficient circulation, as in anæmia, general debility, old age.

It is recommended in diarrhœa of children, and some forms of vomiting caused by imperfect digestion. It is useless for the digestion of carbohydrates and fatty food Pepsin should, however, be used with judgment, for if continued too long it may lead to gastric atrophy. In fact most cases do well without any ferment Pepsin is effective only in the presence of acid, the optimum percentage being

0.4 p.c. The gastric juice is more often deficient in hydrochloric acid, rarely the enzyme, and administration of dilute hydrochloric acid alone will help digestion by converting inactive pepsinogen into pepsin.

Peptone is used for non-specific desensitization in allergic conditions, and 0.5 grm. in cachets has been recommended an hour before meals in urticaria and migraine of gastrointestinal origin which are instances of anaphylaxis. It has also been used in asthma, hay fever, prurigo, eczema and angioneurotic oedema. Injections of peptone once a week have been attended with good results in bronchial asthma by rendering the patient nonsensitive to protein. For intravenous use a 5 p.c. solution in normal saline is used. Begin with 5 ms. and increase with each dose by $2\frac{1}{2}$ ms. unless or until it produces too marked a general reaction. For intramuscular injection a 7.5 p.c. solution is used, commencing with 0.3 c.c. and increasing by 0.2 c.c. to a maximum of 1.5 c.c. which is reached at the 7th dose. These injections are given once or twice a week. Similarly intravenous injection of peptone is useful in various forms of infective fevers (see Protein Therapy).

Prescribing hints—Pepsin may be given in powders, pills, cachets, tablets or capsules. Many of the market preparations are worthless. Being reliable preparations, glycerinum pepsini and liquor pepticus are the best to use. It should be given with, or directly after, meals, either combined with, or followed by, a dose of acid hydrochloric dilute.

PANCREATIN

Pancreatin. (Pancreatin.)

Source.—A preparation of the pancreas, containing the enzymes, trypsin, amylase, and lipase. Prepared from the fresh pancreas of certain animals commonly employed for food, by extraction of one part with four parts of alcohol (25 p.c.).

Characters.—A colourless, or buff-coloured, amorphous powder; odour, meaty. *Soluble* in water, forming a slightly turbid solution; insoluble in alcohol (90 p.c.), and in ether. Should be kept in well-closed containers in a cool place.

B.P. Dose.—3 to 10 grs. or 0.2 to 0.6 grm

NON-OFFICIAL PREPARATIONS

1. **Peptonised Milk**—Dilute 1 pint of milk with 4 ozs. of water and heat to 130° F. (If a thermometer is not at hand, boil one-half of the mixture and add it to the other half.) To this add two teaspoonfuls of liquor pancreatis or 5 grs. of extract pancreatis with 20 grs. sodium bicarbonate and leave the vessel near a fire or hearth for 15 minutes, or in the ordinary temperature of the room for 3 hours. If not used at once, it must be heated to boiling-point. *Pulvis Pancreatini* Co., containing both the extract and soda is more convenient.

2. **Pulvis Pancreatini Compositus, B.P.C. Syn—Peptonising Powder.**—Pancreatin 1 in 5 with sodium bicarbonate. In tubes of 25 grs. each of which is sufficient to peptonise one pint of milk.

3. **Liquor Pancreatini, B.P.C. Syn—Liquor Pancreatis.**—Glycerin of pan-

creatin, about 1 in 6, with sodium bicarbonate, glycerin, alcohol (90 p.c.) and water. *Dose.*— $\frac{1}{2}$ to 2 dr. or 2 to 8 mls.

4. **Trypsin**, B.P.C.—The proteolytic ferment of the pancreas. Converts proteins into peptones in alkaline media. Used for peptonising milk, and in *diabetes*. *Dose.*—3 to 10 grs. or 0.2 to 0.6 gm. in keratin-coated pills.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Pancreatin or Pulvis Pancreatini Co., are best suited for predigesting liquid food before administration in dyspepsia, diarrhoea, and gastric troubles. Children deprived of natural nourishment fare well on pancreatized food. Trypsin and pancreatin, in pills coated with keratin can be given two hours after meals with 20 grs. of sodium bicarbonate. Keratin protects them from the acid of the stomach, but it is doubtful whether the gastric juice becomes so deficient as not to exert any destructive effect on the pancreatic ferment. The value of pancreatic ferment is more problematical than that of pepsin. Pancreatic emulsion is often given with cod-liver oil in wasting diseases when the stomach cannot well digest fat. Pancreatin has been used successfully as a preventive and for treatment of serum disease.

Trypsogen, which is supposed to contain enzymes of the islands of Langerhans is used in diabetes originating from pancreatic functional disturbance, but the results have not been satisfactory. Trypsin has been used in the treatment of cancer, but has hitherto proved a failure. The hypodermic injection of sterilised trypsin solution is combined with its internal administration.

PAPAIN (*Not official*) Prepared from the juice of the unripe fruit of papaw, *Carica Papaya*. In whitish, amorphous, slightly granular powder.

Dose—2 to 10 grs. or 0.12 to 0.6 gm.

NON-OFFICIAL PREPARATIONS

1. **Elixir Papaini**, B.P.C.—Papain 5, alcohol (90 p.c.) 15, water 45, aromatic elixir to 100. *Dose.*— $\frac{1}{2}$ to 1 dr. or 2 to 4 mls with meals.

2. **Glycerinum Papaini**, B.P.C.—Papain 9, Hydrochloric Acid Dil. 8, Simple Elixir 5, Glycerin to 100. *Dose*— $\frac{1}{2}$ to 1 dr. or 2 to 4 mls with meals.

PHARMACOLOGY AND THERAPEUTICS

Papain is used for the same purposes as pepsin and is very useful in cases where there are religious objections to the latter. It is also useful as a vermifuge for ascarides. Locally applied it causes absorption of diphtheritic exudations. The dry powder may be used, or it may be administered in the form of elixir or glycerin.

2. Amylolytic Ferments

EXT ACTU ALTI

Extract of Malt. (Ext. Malt.)

Source.—Prepared from sound, malted grain of barley, *Hordeum distichon*, by digestion with water at a suitable temperature, and by

evaporation of the strained liquid under reduced pressure at a temperature not exceeding 55°, until a viscous product is obtained. Contains nitrogen equivalent to not less than 4.5 p.c. w/w of protein.

Characters.—An amber or yellowish-brown, viscous liquid; odour, agreeable and characteristic; taste, sweet.

B.P. Dose.—60 to 240 ms. or 4 to 16 mils.

OFFICIAL PREPARATION

1. **Extractum Malti cum Oleo Morrhuæ.**—Approximately 15 p.c. v/v cod-liver oil, or 240 ms. contain 36 ms. of cod-liver oil. **B.P. Dose.**—60 to 240 ms. or 4 to 16 mils.

NON-OFFICIAL PREPARATION

1 **Diastase, B.P.C. Syn—Amylase**—A mixture containing amylolytic enzymes obtained from an infusion of malt. Converts not less than 50 times its weight of potato starch into sugar. In yellowish-white, amorphous powder, or in translucent scales. Odourless and tasteless. **Dose.**—1 to 5 grs or 0.06 to 0.3 grm.

PHARMACOLOGY AND THERAPEUTICS

The various malt extracts, are valuable as foods for persons suffering from *wasting diseases*, such as phthisis, as they are easily tolerated by the stomach, and maltose leads to the formation of fat. Being sweet they may be used either alone or combined with cod-liver oil. Malt is a good source of vitamin B.

Powdered malt in combination with baked wheaten flour in varying proportions forms most of the popular infant's foods. It may also be taken mixed with milk or beer or sprinkled over porridge, but as diastase only acts in an alkaline medium it is best to give malt two hours after a meal. It is doubtful if it exerts any appreciable effect in promoting carbohydrate digestion.

TAKA DIASTASE (*Not official*)—An enzyme obtained from a species of *Eurotium oryzae*, cultivated on bran. A yellowish-white powder, which changes in a few minutes a hundred times its weight of starch into maltose.

Dose.—1 to 5 grs or 0.06 to 0.3 grm.

PHARMACOLOGY AND THERAPEUTICS

It is very valuable in all forms of starchy dyspepsia with hyperacidity such as are common amongst the rice-eating inhabitants of Bengal, and it will be found *preferable to pepsin in all cases of this kind*. It may be combined with sodium bicarbonate.

CLASS C: Emetics

Vomiting is a complex physiological phenomenon to produce which several parts are brought into play. The chief of them is the vomiting centre in the medulla and the afferent stimuli carried to the centre from various sources. The centre may be excited *directly* by disturbances in the cranial circulation (anæmia of the brain), or by mechanical and chemical stimuli, *e.g.* pressure due to growth, meningitis, uræmia, etc.; or *indirectly* by certain peripheral stimuli, *e.g.* various unpleasant sensations, repulsive sight, offensive smell, acute pain (renal colic), disturbances of the labyrinth (sea-sickness), and by certain drugs and poisons.

Emetics are drugs which produce vomiting. This is often accompanied by nausea, salivation, sweat, secretion of mucus from the air passages and œsophagus, quick pulse and irregular respiration. During the act of vomiting the cardiac sphincter opens and the pyloric

portion of the stomach tightly contracts, and the contents of the stomach are expelled by a simultaneous contraction of the abdominal muscles and the diaphragm. The co-ordination of all these movements is controlled by the vomiting centre.

(1) *Local or Reflex Emetics*, also called *Gastric Emetics*.—These cause vomiting by stimulating the sensory endings of the vagus in the stomach. They act only when they reach the pyloric end of the stomach, and therefore act better when used with a large bulk of water for rapid action, as they then reach the pyloric end rapidly. They are often used in cases of poisoning, but being irritants they have an injurious effect if emesis does not occur. All gastric irritants act as emetics. Thus vomiting is a common accompaniment of almost all irritant poisons. The emetics are—zinc sulphate, alum, ipecacuanha, emetine, carbonate of ammonia, copper sulphate, tartar emetic, mustard, common salt, warm water.

(2) *Central Emetics*.—These act by stimulating the vomiting centre after absorption. As apomorphine.

Digitalis, morphine and lobeline also cause vomiting by stimulating the centre.

Therapeutics.—Emetics are used (1) to remove foreign bodies from the throat and œsophagus; (2) to expel undigested substances and poisons from the stomach; (3) to increase secretion of bronchial glands, in small doses; and (4) sometimes to aid the action of antiperiodics.

They are *contra-indicated* in hernia, aneurism, prolapse of the rectum and uterus, peritoneal and intestinal inflammation, and in cases of threatened abortion, or when there is tendency to hæmorrhage or atheroma of vessels.

CLASS D: Antiemetics

These are drugs which are used to stop vomiting. They may act locally, when they are called *direct antiemetics*, or centrally. Examples of central vomiting are sea-sickness, vomiting of pregnancy, cyclic vomiting and vomiting due to passage of calculus through the ureter or bile duct. Prevention of central vomiting is rather difficult. Atropine counteracts the vomiting due to morphine and pyloric spasm. Bromides and chloral hydrate in large doses depress the centre. Amyl nitrite and nitroglycerin are sometimes useful. The common antiemetics are, small doses of adrenaline, alcohol, calomel and arsenious acid; drop doses of solution of iodine or tincture of ipecacuanha; hydrocyanic acid dilute, carbonic acid, cerium oxalate, cocaine, chlorbutol, creosote, ice, hot water and bismuth salts.

ACID HYDROCYANIC

(Acid. Hydrocyan. Dil.)

Dilute Hydrocyanic Acid. HCN

Syn.—Diluted Hydrogen Cyanide; Dilute Prussic Acid.

Source.—An aqueous solution containing 2 p.c. w/w of hydrogen cyanide; prepared by the interaction of dilute sulphuric acid and potassium ferrocyanide.

Characters.—A colourless, volatile liquid with characteristic odour; sp. gr. 0.997; faintly acid.

Incompatibles.—Copper, iron and silver salts, red mercuric oxide and sulphides.

B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil.

PHARMACOLOGY

Externally.—Hydrocyanic acid is a protoplasmic poison and is absorbed from the epidermis, but more readily from

a raw surface. It paralyses the periphery of the sensory nerves, and thus acts as a local sedative and anæsthetic.

Internally. **Alimentary canal.**—It has an acrid bitter taste and causes burning and reflexly salivation followed by numbness in the mouth and throat. It is absorbed rapidly by the mucous membrane, and has the same action in the stomach as on the skin, *i.e.* depresses the sensory nerve terminations. It is therefore a gastric sedative and relieves pain.

Blood.—It quickly enters the blood from all parts of the body and in poisoning it destroys the oxidase and prevents the cells from utilising the oxygen from the blood, consequently the oxyhæmoglobin is not reduced in the capillaries, with the result that the venous blood is found scarlet red and the tissues suffer from oxygen starvation. If however death is delayed, or the dose is not lethal, the acid is changed to harmless products in the tissues, which enable the protoplasm to recover its oxygen-absorbing power; the expired air becomes less rich in oxygen and contains more carbonic acid, and the venous blood regains its usual dark purple colour.

Heart and blood-vessels.—A small dose stimulates the vagal centre and slows the pulse. A large dose at once arrests the heart in diastole, due to direct action on the cardiac centre, and on the nervo-muscular apparatus of the heart, for it has been observed that hydrocyanic acid stops the heart's action even when topically applied. The blood pressure is first momentarily heightened and afterwards deeply lowered from a transitory stimulation and subsequent paralysis of the vaso-motor centre.

Respiration.—It is excreted by the bronchial mucous membrane and depresses the sensory endings thus acting as a sedative and reduces cough. A small dose makes the respiration quicker and deeper, but is soon followed by depression when respiration becomes feeble and laboured and death takes place from asphyxia, except in those cases where the heart is instantly stopped by a large dose.

rain.—Medicinal doses have no action. Large doses cause insensibility and coma, referable either to the direct action of the drug on the cerebrum or to the altered conditions of blood from asphyxia. Pupils are dilated. Convulsions do not occur in man, but are common in animals.

edulla and cord.—Small doses stimulate the vagal, vaso-constrictor and respiratory centres for a brief period, but a large dose paralyses the respiratory, vasomotor and cardiac centres. The reflex excitability of the cord is first lowered and then abolished altogether. The peripheral sensory nerves are less affected by internal administration than by local application. The motor nerves and muscles are also paralysed.

Elimination.—Hydrocyanic acid is rapidly excreted, chiefly by the breath. It is also partly changed to sulphocyanides, which are excreted in the urine.

Acute toxic action.—It is hardly ever used for criminal poisoning, but because of its quick action it is often employed for suicidal purpose. Poisoning also may occur from inhalation of the gas used in fumigation. If the dose be large, it is followed almost instantaneously by a gasping cry, a few convulsive movements and death. But with a smaller dose, the patient becomes unconscious; his eyes fixed; pupils dilated; pulse, feeble and irregular or imperceptible; respiration, slow, deep and convulsive with frothing at the mouth; skin, cold and clammy and at last death occurs. At the *post mortem* are found the odour of hydrocyanic acid, lividity of the surface, clenched fingers, firmly closed jaws, froth at the mouth, fixed and glistening eyes, dilated pupils, dark blood, and slightly congested stomach.

Treatment.—Because of its rapid action treatment of cyanide poisoning is very limited. Whenever possible attempt should be made to evacuate the poison or to destroy the poison in the stomach. Animal charcoal, hydrogen peroxide, permanganate of potassium (1 in 1000), or sodium thiosulphate 5 p.c. should be given promptly followed by lavage with one of these solutions diluted 1 in 10. Artificial respiration or 5 p.c. CO_2 with oxygen. Fall of pressure should be treated with adrenaline. Sodium nitrite 1 p.c. solution should be injected in 10 c.c. doses intravenously up to 50 c.c. in an hour, alternating with sodium thiosulphate 5 p.c. in 20 c.c. doses up to 500 c.c., or methylene blue 1 p.c. in isotonic (1.8 p.c.) sodium sulphate, 50 c.c. at a time up to 500 c.c. if necessary. For cyanosis transfusion of blood.

Fatal Dose.—1 gr. or 0.05 grm. of pure HCN; 3 to 5 grs. or 0.2 to 0.3 grm of KCN.

THERAPEUTICS

Externally.—Dilute hydrocyanic acid is rarely used now. It removes the itching of urticaria, lichen and dry eczema, when the affected parts are bathed or sponged with a lotion (2 drs. to 8 ozs. of rose water and glycerin). Care should always be taken not to apply the ointment or lotion to a raw surface.

Internally.—For irritative gastric disorders and dyspepsia it is ordinarily prescribed with sodium bicarbonate and bismuth as a gastric sedative. It is also used to stop vomiting of dyspepsia, gastric ulcer and of pregnancy in 1 to 2 ms. doses and to relieve the hacking cough of phthisis, and the spasms of hiccough. For this purpose it is generally used either in the form of syrup of wild cherry (see page 316), or tinct chloroformi et morphinæ co.

Prescribing hints.—For its sedative effect on the stomach, dilute hydrocyanic acid may be combined with sodium bicarbonate and given either as an effervescing draught, or combined with carbonates of bismuth and magnesium.

CLASS E : Adsorbents

Charcoal, Kaolin (*see* Page 132), Magnesium Trisilicate (*see* page 104)**CA O LIGNI**

Wood Charcoal. (Not official)

Source and Characters.—A black powder, free from grittiness, prepared by exposing wood to a red heat without access of air.

Dose—60 to 120 grs or 4 to 8 gms

PHARMACOLOGY AND THERAPEUTICS

If we dissolve a dye in distilled water and pass it through finely powdered charcoal we find that most of the colour disappears. No chemical reaction has taken place, but the powdered charcoal has a large surface, and the action of this upon the dissolved particles of dye has made these accumulate or condense upon the surface of the charcoal by process of adsorption. This property is taken advantage of in the therapeutic uses of charcoal.

Externally.—Dry charcoal adsorbs and condenses gases within its interstices, specially oxygen, which it parts with to oxidise organic and other substances either liquid or gaseous. Hence it acts as a disinfectant and deodorant. It may, by giving off oxygen, help the growth of anaerobic organisms. In the same manner it adsorbs colloidal impurities, proteins, etc. The process of adsorption, being a surface action, is a purely physical phenomenon and the effect is greatest when the surface is very large, *i.e.* the particles are very small, or the surface has been made greater by porosity.

Internally.—It exerts the same adsorptive power in the stomach and intestine and therefore it is used in cases of poisoning by phosphorus, alkaloids, etc., and as it prevents the absorption of the poison its use should be followed by an aperient, preferably a saline, to expel the contents. Alone or combined with kaolin, which also acts in the same way, it is used in diarrhoea, dysentery and cholera, where it acts by checking bacterial growth and by adsorption of irritating putrefactive products.

Charcoal may be used in powder, cachets or lozenges either alone or combined with bismuth carbonate and betanaphthol in the treatment of flatulence and acid dyspepsia. To increase the adsorptive power charcoal is activated by heating to a high temperature in steam or other activating gas and then washing and drying.

DRUGS ACTING ON THE INTESTINE

We have already seen that the acid chyme from the stomach enters the duodenum in driblets and Mellanby has shown that the presence of this liberates a hormone which excites the contraction of the gall-bladder so that a certain amount of bile enters the duodenum. The bile acids and their products of decomposition are partly absorbed and help the formation of secretin which stimulates both the pancreatic secretion and bile. Therefore the chyme is subjected to a further process of digestion by the secretion from the liver, the pancreas and the intestinal glands. The chyle and other soluble ingredients are absorbed by the lacteals and the portal veins as the chyme is propelled downwards by the intestinal movements.

Four kinds of movements, *viz.* *pendulum*, *rhythmic segmentation*, *peristaltic* and *vermiform*, occur in the intestine. The pendulum movements consist of rhythmic contraction and relaxation and is due to the spontaneous rhythmic action of the longitudinal muscle and takes place even in the isolated pieces of the gut. They move the contents backwards and forwards. Rhythmic segmentation helps

to soften and mix the contents. It is essentially a series of local contraction of the circular muscle and occurs at those portions where the food mass is lodged, and is possibly due to local distension caused by the food. The peristaltic movements occur every three or four minutes and pass down the intestine carrying the contents downwards. They are excited reflexly by stretching and chemical stimuli. The vermiform movements are irregular and are confined to the colon.

Absorption is carried on by osmosis and diffusion, and excretion partly by osmosis and partly by the glands, which furnish the succus entericus. The excretion particularly of the watery portion is so profuse, that the effect of absorption is neutralised, and the contents of the small intestine and the duodenum remain liquid. In addition to this, certain micro-organisms, whose normal habitat is the intestinal tract, play an important part in the intestinal digestion. They may occasionally give rise to toxins and so produce symptoms of considerable gravity.

The absorption from the gut varies. Substances not soluble in water and lipoids are not absorbed at all, while the soluble ones are usually absorbed, though the lipoid-soluble substances more easily than the water-soluble ones. Absorption takes place from the small intestine, and the rate of absorption of water-soluble substances depends upon the rate of diffusion, which in its turn depends on the size of the molecules. True colloids like proteins and starch, are not absorbed, but soaps and alkaloids which are semi-colloids are rapidly absorbed.

The colon has a lower absorptive power than the small intestine. Sugar and salts are absorbed from the colon. Drugs that are absorbed by the intestine are as a rule absorbed when given per rectum, but more slowly. But substances which depend for their absorption upon the changes produced by the digestive juices are not absorbed when given per rectum. Many drugs however act quickly and strongly when administered per rectum.

The muscular coat of the gut is supplied by the sympathetic system through the splanchnic nerves, the stimulation of which causes inhibition and therefore arrest of movements, except the ileo-cæcal and the internal anal sphincters, and the muscularis mucosæ, to which the fibres are motor. The vagus (parasympathetic) supplies the motor or augmentor nerves, the stimulation of which increases the tone of the intestine and renders the movements more active but relaxes the sphincters. The peristalsis is essentially independent of extrinsic nervous influences. The Auerbach's plexus (which lies between the circular and longitudinal muscular coat) acts as the excitor neurone of the vagus in the intestine. The vagus supplies the motor nerve to the whole of the small intestine and also part of the colon, and the pelvic nerve supplies motor fibres to most of the colon and the rectum.

Intestinal Movements.—The intestinal movements are influenced by many drugs through the nervous mechanism, or through irritation of the mucous membrane, *e.g.* irritant purgatives.

1. *The movements are increased by* (1) parasympathetic stimulation, *e.g.* by pilocarpine, physostigmine, lobeline and acetyl-choline. These act through the vagus endings independently of the Auerbach's plexus and the sympathetic apparatus. Choline being normally present in many tissues, it is generally believed that it assists in maintaining the activity of the gut. (2) Acting directly on the muscle, as pituitary extract, lead and barium salts and histamine. Rarely by digitalis and hormonal (extract of spleen). Strychnine acts on the muscle and by stimulating reflex excitability of Auerbach's plexus.

2. *The movements are diminished by* (1) nicotine which stimulates the sympathetic ganglia; (2) adrenaline, stimulating the sympathetic endings, possibly opium; (3) atropine and hyoscyne, by depress-

ing the vagus (parasympathetic); (4) papaverine, benzyl benzoate, nitrites, volatile oils and chloroform, by acting locally on the muscles; and (5) bismuth salts, calcium and kaolin, by acting as mechanical protectives.

Violent and irregular intestinal movements occur in colic and are relieved by belladonna and opium. Belladonna is often combined with purgatives to check irregular movements of the gut and griping. In intestinal paresis pituitary extract and physostigmine are used subcutaneously. The movements are inhibited by anæsthetics or reflexly through the sympathetic. Any interference with the peritoneal cavity is followed by inhibition, as for instance post-operative paralysis of the intestine after abdominal operation.

Intestinal Antiseptics.—Since in most bacterial infections of the intestine the colon and the lower part of the small intestine are involved, intestinal disinfection implies disinfection of these parts. The seat of infection may be in the bowel wall itself, or the septic process may occur in the contents of the intestine. In either case the results have been disappointing and a drug strong enough to produce any bactericidal effect has an injurious action on the tissues of the gut. Intestinal antiseptics should possess the following qualities, viz.—(1) should be relatively non-toxic even if absorbed; (2) should act in an alkaline medium and in the presence of organic matter; (3) should not be destroyed in the upper part of the intestine and should have no injurious effect on the intestinal mucous membrane; and (4) should not interfere with the normal bacterial action of the intestinal mucosa. Such an ideal antiseptic is difficult to obtain and the so-called antiseptics have no such effect. In fact Schutz has shown that the healthy intestinal mucosa, which normally possesses germicidal action like other mucous membrane, becomes devoid of this property by the use of antiseptics and purgatives. Intestinal disinfection therefore is very difficult to produce, and it has been found almost impossible to cause even a diminution of the bacterial growth with certainty. Being slightly soluble, salol has often been used, which splits into phenol and salicylic acid in the gut. Salicylic acid, menthol, naphthol and thymol have been found effective experimentally. Fatty acid ester of thymol has been found effective in certain infections. Calomel is largely used as intestinal antiseptic; it acts not by any bactericidal action but by expelling the putrefying contents of the gut. Drugs which adsorb bacteria and toxins are sometimes more useful than many of the reputed intestinal disinfectants. Thus kaolin, which forms a coating on the whole of the intestinal mucosa, is used in the treatment of cholera and by its adsorbent effect prevents absorption of toxins. By irrigation of the colon with antiseptics some disinfection can be produced locally.

GROUP IX

PURGATIVES

Purgatives, Cathartics, Evacuants, or Aperients are drugs which cause evacuation of the bowels. The act of defæcation is accompanied by increased peristaltic contraction of the rectum and opening of the internal sphincter of the anus. It is not possible to definitely ascertain what normal impulse in the rectum produces the initial reflex for defæcation, possibly a certain amount of fullness and consistency of its contents form the necessary stimulus. Purgatives act either (a) by increasing the volume of the non-absorbable material; (b) by preventing the absorption of water; (c) by irritating the small and large intestine, and thus reflexly increasing peristalsis; and (d) by stimulating the neuro-muscular mechanism directly. The contents of the small intestine are poured out through the ileo-cæcal valve in an almost fluid condition, and the formation of the fæcal

masses takes place during their long stay in the large intestine. A drug, therefore, which would simply increase the peristaltic movements of the intestine may give rise to watery evacuation by hurrying the contents into the rectum without giving time for absorption of the fluid; on the other hand the accumulation of a large quantity of fluid in the intestine reflexly excites peristalsis.

Many drugs cause looseness of the bowels, but since they act as powerful irritants they are not used as purgatives. An ideal purgative should not have any other effect except on the intestines, it should not irritate the stomach, but should become active only when it reaches the intestine. It should not be easily absorbed or absorbed so slowly that it can exert its effects throughout the intestine.

Some purgatives act mechanically, due to their bulk, and distending the bowel reflexly induce the need of evacuation. They are harmless and non-irritant and may be continued for a long time without any disadvantage. They are useful in habitual constipation and in cases where there is a deficiency of sufficient ballast to form the faecal mass. Chief of these are agar-agar, cereals, liquid paraffin, ispaghula, Bael, etc.

Purgative oils like castor oil, or croton oil become active only when the fatty acids are liberated; the anthracene purgatives act after the glycosidal compounds are split up; while the resinous purgatives, after the resins are decomposed and dissolved by alkalis and bile. Bile therefore is necessary for most resinous purgatives like podophyllum, jalap, etc.

Different purgatives act on different parts of the intestine. Castor oil, for instance, acts on the small intestine, having little or no effect on the colon, although Hurst has shown that in man it stimulates both the small and large intestines. Aloes, senna and other anthracene purgatives act entirely on the large intestine without producing any effect on the movements of the stomach and small intestine. They, therefore, take longer time to act. The drastic purgatives increase the peristalsis of both the large and small intestines, and in large doses cause accumulation of fluid within the intestine. Magnesium sulphate hastens the passage through the small intestine and prevents the absorption and helps concentration of the contents in the large intestine. Calomel stimulates the peristalsis of both the small and large intestines.

Atony of the muscles of the intestine follows the use of most purgatives with consequent after-constipation. This effect is more marked after castor oil and rhubarb which contains rheo-tannic acid.

Some purgatives cause evacuation when given subcutaneously, while croton oil when rubbed on the skin also acts as a purgative. Senna, aloes and colocynth belong to the former group. But these effects are not due to any specific action on the bowel but in all probability result from their excretion into the intestine. Others again, not ordinarily used as purgatives, act as such when given subcutaneously by their special selective affinity on the nervous system or muscle. To this class belongs pilocarpine, acetyl-choline, and physostigmine which act by stimulating the vagus endings; apocodeine ($\frac{1}{2}$ gr.) and ergotoxine ($\frac{1}{8}$ gr.) by depressing the ends of the splanchnic or inhibitory nerves. Pituitary extract acts on the muscle directly.

Therapeutics—The purgatives are used (1) to remove faecal accumulation in cases of constipation; (2) to drain serum from the blood in cases of cardiac, renal and hepatic dropsies; (3) to lower the temperature in fevers; (4) to lower the blood-pressure in apoplexy and cerebral congestion; (5) to prevent straining in persons suffering from piles, aneurism or hernia; (6) to expel bile and help the passage of biliary calculi; (7) to remove from the blood certain excrementitious matters, such as urea, uric acid, etc.; and (8) to

remove irritating or otherwise harmful substances from the intestine as in food poisoning, intestinal putrefaction, and in diarrhoea due to undigested food material.

Contra-indications.—Purgatives should not be used at all or used with caution in

1. Inflammatory conditions of the abdominal organs, peritonitis, enteritis, etc.
2. During pregnancy and menstruation, when strong purgatives should be avoided.
3. Intestinal hæmorrhage, prostration and collapse.
4. Intestinal obstruction and intussusception.

The purgatives are classified as follows:—

Class A Those acting by increasing the volume of non-absorbable material in the intestine

- 1 Whole Meal Bread, Fruits, Oat Meal, Agar, Paraffin, Isuphgul (*q v*), Bael (*q v*)
- 2 Saline purgatives, these act by interfering with absorption
Sulphate and Phosphate of Sodium, Acid Tartrate of Potassium, Sodium Potassium Tartrate, Sulphate, Carbonate and Oxide of Magnesium.

Class B Those acting as irritants

- 1 Laxatives Tamarinds, Cassia, Manna, Castor Oil, Sulphur (*q v*)
- 2 Anthracene purgatives Aloes, Rhubarb, Senna, Cascara, Phenolphthalein
- 3 Diastolic purgatives Scammony, Jalap, Croton Oil, Colocynth, Kaladana (*q v*), Turpeth (*q v*)
- 4 So-called cholagogue purgatives These do not act by increasing the secretion of bile but increase its excretion by hurrying the contents of the intestine by increasing peristalsis and thus preventing reabsorption. They are Podophyllum, Euonymus, Iridin, Mercurials.

Class C Pilocarpine, Physostigmine, Pituitary extract, Acetyl-choline, Apocodeine and Hormonal, when given hypodermically stimulate the motor nerves or the muscle and act as purgatives. These are not ordinarily used as purgatives

1. SALINE PURGATIVES

POTASSII TART AS ACI US

Acid Potassium Tartrate. (Pot Tart. Acid). $\text{KC}_4\text{H}_5\text{O}_6$

Syn.—Purified Cream of Tartar; Potassium Bitartrate.

Source.—Prepared by the purification of the deposit obtained during the fermentation of grape juice. Contains not less than 99.5 p.c. of pure potassium hydrogen tartrate.

Characters.—In gritty, white crystalline powder, or colourless, slightly opaque crystals. Taste, pleasant and acid. *Solubility.*—1 in 220 of water, not in alcohol (90 p.c.).

B.P. Dose.—15 to 60 grs or 1 to 4 grm.

Enters into.—Conf. Sulph., Pulv. Jalap. Co.

NON-OFFICIAL PREPARATION

1. Potus Imperialis, B.P.C. *Syn.*—*Imperial Drink.*—Acid pot tartrate 40 grs, citric acid 7 grs, sucrose 1 oz, oil of lemon 3 ms, tinct of lemon 50 ms, water q s. 20 oz

SO II ET P TASSII TA T AS

(Sod. et Pot. Tart.)

Sodium Potassium Tartrate. $\text{KNaC}_4\text{H}_4\text{O}_6, 4\text{H}_2\text{O}$

Syn.—Soda Tartarata; Rochelle Salt; Seignette's Salt.

Source.—Neutralise acid potassium tartrate with sodium carbonate. Contains not less than 99 p.c. pure sodium potassium tartrate.

Characters.—Colourless crystals, or a white crystalline powder; taste, saline and cooling. *Soluble* in 1.5 parts of water, forming a clear, colourless solution; almost insoluble in alcohol (90 p.c.).

B.P. Dose.—120 to 240 grs. or 8 to 16 grm.

OFFICIAL PREPARATION

1. **Pulvis Effervescens Compositus.** *Syn.*—*Pulvis Sodæ Tartaratæ Effervescens; Seidlitz Powder.* **B.P. Dose.**—Dissolve No. 1 powder in a tumbler of cold or warm water; add No. 2 powder. To be taken while effervescing.

SO II SULP AS

Sodium Sulphate. (Sod. Sulph.). $\text{Na}_2\text{SO}_4, 10\text{H}_2\text{O}$

Syn.—Glauber's Salt.

Source.—Obtained by the interaction of sodium chloride and sulphuric acid.

Characters.—In colourless, odourless crystals; taste, bitter and saline. Efflorescent in dry air *Soluble* in 3 parts of water, insoluble in alcohol (90 p.c.).

B.P. Dose.—30 to 240 grs. or 2 to 16 grm.

OFFICIAL PREPARATION

1. **Sodii Sulphas Effervescens.**—**B.P. Dose**—60 to 240 grs. or 4 to 16 grm.

NON-OFFICIAL PREPARATION

1. **Sal Carolinum Factitium, B.P.C.** *Syn.*—*Artificial Carlsbad Salt.*—Sodium Sulphate 55, Potassium Sulphate 1, Sodium Chloride 10, Sodium Carbonate 35 *Dose*— $\frac{1}{2}$ to $1\frac{1}{2}$ drs. or 2 to 6 grms. in warm water. 0.5 p.c. solution resembles *Carlsbad water.*

SO II P OSP AS

Sodium Phosphate. (Sod. Phosph.). $\text{Na}_2\text{HPO}_4, 12\text{H}_2\text{O}$

Syn.—Di-sodium Hydrogen Phosphate Tasteless Purging Salt.

Source.—Prepared by the interaction of sodium carbonate and acid calcium phosphate. Contains not less than 99 p.c. of pure di-sodium hydrogen phosphate.

Characters.—Colourless, efflorescent, crystals. *Solubility.*—1 in 7 of cold water.

B.P. Dose.—30 to 240 grs. or 2 to 16 grm.

OFFICIAL PREPARATION

1. **Sodii Phosphas Effervescens**—**B.P. Dose.**—60 to 240 grs. or 4 to 16 grm.

S II P OSP AS ACI US

(Sod. Phosph. Acid.)

Acid Sodium Phosphate. $\text{NaH}_2\text{PO}_4, 2\text{H}_2\text{O}$

Syn.—Sodium Di-hydrogen Phosphate; Sodii Biphosphas, U.S.P.

Source.—Obtained by the combination of sodium phosphate with phosphoric acid. Contains not less than 98 p.c. of pure sodium di-hydrogen phosphate.

Characters.—Colourless, crystals, or a crystalline powder. Taste, saline and acid. *Soluble* in 1 part of water.

B.P. Dose.—30 to 60 grs or 2 to 4 grm.

AGNESII SULPHAS

Magnesium Sulphate. (Mag. Sulph.). $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$

Syn.—Epsom Salts.

Source —Prepared by the interaction of magnesium carbonate and diluted sulphuric acid.

Characters.—Colourless crystals; odourless. Taste, cool, saline and bitter. Effloresces in dry air. *Soluble* in 1.5 parts of water, sparingly soluble in alcohol (90 p.c.).

B.P. Dose—30 to 240 grs. or 2 to 16 gm.

PHARMACOLOGY OF SALINE PURGATIVES

Under this head are included the sulphate and phosphate of sodium, the acid-tartrate of potassium, sodium potassium tartrate, and sulphate of magnesium, which, because of their low absorbability from the intestinal tract, disturb the osmotic balance between the bowel contents and the surrounding tissues. It has been found that certain salts are absorbed readily through the intestinal tract, and this depends upon the nature of the ions of which they are composed. Among those that are absorbed very slowly are the cations, calcium, magnesium, and the heavy metals; and the anions, phosphates, sulphates, tartrates, citrates, etc. Of these magnesium among the basic, and citrates, phosphates, tartrates and sulphates among the acid ions have cathartic properties. When both ions are slowly absorbed the effect is more powerful, *e.g.* magnesium sulphate is a stronger purgative than sodium sulphate, because the sodium ion is more easily absorbed than the magnesium ion, sulphate ion being common in both the salts. As a rule salines do not irritate the gut like the vegetable purgatives unless given in large doses. The action of saline purgatives is due not to irritation but to retarded absorption.

Solutions of these salts have an unpleasant salt taste, and when used in a concentrated form, they irritate the stomach and may produce nausea. If they remain longer they promote transudation and secretion and therefore help their own dilution. By means of a cæcal fistula it has been shown that if an isotonic salt solution and a solution of sodium sulphate be administered by the mouth, little or none of the former reaches the cæcum, while most of the latter solution escapes by the fistula, only about 10 to 20 p.c. being absorbed by the stomach and intestine above the fistula. It is evident therefore that if any of the cathartic salts be used, from 80 to 90 p.c. of the fluid reaches the large intestine where it remains unabsorbed. The catharsis is due to the large bulk of the fluid which distends the bowel and which induces increased peristalsis. The intensity of action of these salts depends upon the concentration of the solution in which they are administered. For instance, if the salt is freely diluted more of the fluid is absorbed and

less reaches the large intestine. Whereas if the solution be hypertonic it will draw fluid from the blood into the intestine, due to its higher osmotic pressure, and the blood gives up its fluid without any sufficient compensation of salt until the solution becomes isotonic. A large amount of fluid thus accumulates with the resultant evacuation. Boas on the other hand asserts that the catharsis is less powerful when the solution used is more concentrated, and that the salt is more prone to be absorbed and to produce systemic effects. He reports several cases of poisoning from concentrated doses of magnesium sulphate. It must be borne in mind that purgation is produced only if the intestine is able to furnish a sufficiently large amount of fluid, which depends upon the amount of water present in the blood and tissues. It takes a longer time to produce purgation if a hypertonic solution is used, as its entrance into the duodenum causes closure of the pylorus, and the dilution results practically only from gradual secretion of the digestive juices unless some water is taken at the same time. It may therefore take many hours before the quantity becomes large enough to produce an evacuation. A dilute solution on the other hand may cause liquid stool, provided a large amount of it rapidly passes into the large bowel. If however there be no evacuation, the salt is absorbed into the blood and excreted by the kidneys and acts as a diuretic. MacCallum has suggested that salines act by precipitating calcium in the tissues and so neutralise its depressing action. The stool generally consists of

- (1) the salt and the fluid derived by transudation, and
- (2) some of the unabsorbed gastro-intestinal contents.

Bayliss and Starling have shown that the passage of liquids along the intestine is different from that of solid or pasty matter. Whereas solids stimulate peristalsis, liquids simply generate rhythmic intestinal segmentations; the result being that while the liquids pass along, more or less of the solid contents of the intestine are liable to be left behind. Hay has shown that when sulphate of magnesium is used for a long time it is excreted as sulphate in the urine in combination with sodium and potassium, thus reducing the alkali reserve of the body.

THERAPEUTICS OF SALINE PURGATIVES

The saline purgatives are extensively used in cases of constipation, chiefly habitual constipation, as by increasing the fluidity of the intestinal contents they facilitate the expulsion of hard and dry faeces. They are however of little use in spastic constipation. They are taken freely diluted in warm water, first thing in the morning, or the sulphate or the tartrate may be taken in the effervescent form. Sodium

sulphate is the active principle of many natural mineral waters, e.g. *Carlsbad*, *Marienbad*, *Tarasp*, and *Condal* waters, while in combination with magnesium sulphate it occurs in *Aesculap*, *Hunyadi Janos*, *Pullna*, *Apenta* and *Kissingen* waters. *Friedrichshall* water contains sodium chloride in addition to the above mentioned ingredients. These mineral waters may be taken with advantage in chronic constipation. When a complete evacuation is required they are generally combined with some vegetable purgative, as pulvis jalap. co., mistura sennæ co. When we want to drain out fluid from the body as in dropsy, pleurisy, ascites, etc., salines are either used in concentrated solutions (magnesium sulphate dr. 5 in oz. 1 of water), or given with some drastic purgative like jalap, where the effect of the latter drug reinforces the hydragogue action. As these salines are not cleansing, it is customary to precede their use by a vegetable or mercurial purgative. The usual practice is to give a dose of calomel or blue pill at night and to follow it up in the morning with a dose of black draught, Seidlitz powder, Glauber's salt, Epsom salt, or some natural mineral water. Saline purgatives are extremely valuable in relieving portal congestion, and constipation associated with gout and uric acid diathesis.*

Sulphate of soda is considered almost a specific in **bacillary dysentery**, and being less irritating than the sulphate of magnesium, is largely used in this disease. Sometimes the two salts are combined together.† Epsom salt is an excellent purgative to counteract the constipating effect of iron in the treatment of anæmia

In many cases the saline purgatives reduce the febrile temperature, and although they have no special action as intestinal antiseptics, they often reduce intestinal putrefaction by expelling the decomposing fæcal matter.

The different mineral waters are often used daily to reduce body weight and to lower blood-pressure. In the form of imperial drink the acid potassium tartrate is largely used by fever patients as a cooling and refreshing drink.

Sodium phosphate being mild and almost tasteless is suitable for a delicate stomach and for administration to children. Acid sodium phosphate being the natural acid of the urine, is largely used to render the alkaline urine acid in 30 gr. doses. It is successfully used in the treatment of

*R

Sod et pot. tart.	oz 1½
Sod sulph	oz 1½
Mag carb.	grs 240
Sod bicarb.	oz 1
Ol. menth pip.	ms 10

One teaspoonful or more in half a tumbler of water in the morning

†R

Sod sulph.	
Mag. sulph aa	grs 60
Tinct opii camph	ms 20
Syl aurant	ms 60
Aq. menth pip. dest ad	oz 1

oxaluria and cystitis, particularly when due to *B. coli* infection.

2. Laxatives

AGA

Agar

Syn—Agar-agar.

Source.—A dried gelatinous substance obtained from *Gelidium corneum*, *G. cartilagineum*, and other closely allied Rhodophyceæ.

Characters—In slender, translucent, nearly colourless, lustrous strips, 4 millimetres wide, or flattened yellowish bands about 4 centimetres wide, or a greyish-white powder; swells to a gelatinous mass when immersed in water. *Insoluble* in cold water, soluble when boiled with 100 parts of water, the solution forms a stiff jelly on cooling.

B.P. Dose.—60 to 240 grs or 4 to 16 grms.

PHARMACOLOGY AND THERAPEUTICS

Agar is largely used for preparing culture media for bacteriological purposes. It is tasteless, and when boiled with water or milk (1 in 200) forms into a jelly which may be given to invalids as food. Given internally mixed with milk, fruits or any other vehicle it is not absorbed and passes through the intestinal canal almost unchanged, only about 8 to 27 p.c being utilised. During its passage through the gut it draws moisture and increases in bulk which stimulates peristalsis and acts as a mild laxative, making the stool soft and bulky. It is valuable in habitual constipation, and may be combined with liquid paraffin or cascara.

TA A IN US

Tamarind. (Tamarind.)

Source—Consists of the fruits of *Tamarindus indica*, freed from the brittle outer part of the pericarp, and preserved with sugar.

Characters.—A reddish-brown, moist, sugary mass, containing strong fibres, and brown shining seeds, each enclosed in a membranous coat. Taste, sweet and acid; odour, fragrant and fruity.

Composition.—(1) *Tartaric acid*, 10 p.c and *acid potassium tartrate*, 8 p.c
(2) *Citric, acetic* and other acids (3) *Invert sugar*, 25 to 40 p.c

Enters into.—Confectio sennæ.

PHARMACOLOGY AND THERAPEUTICS

As a refrigerant, tamarind whey (tamarind 1, milk 30) is given as a drink in fevers. It is a mild laxative, and when spread on bread and butter forms a pleasant purgative for children.

CASSIA

Cassia. (Cass.)

Syn—Cassia Pulpa. **Syn** I.V.—*Sondaler ata*, Beng. *Amaltas*, Hind

Source.—The pulp obtained from the *Cassia Pods* by percolation with water, and evaporation on a water bath to the consistence of a soft extract.

Composition —(1) A *Purgative principle* allied to cathartic acid (2) *Sugar*, about 50 p c

B P Dose —60 to 120 grs. or 4 to 8 grm.

Uses —Cassia pulp is never given alone on account of its griping properties, but with senna in the form of confection of senna.

MANNA (*Not official*) The dried saccharine exudation of an ash-tree *Fraxinus Ornus*. Contains *mannitol* the hexahydric alcohol *mannotriose*, *mannotriose*, dextrose, mucilage, starch, etc

Dose — $\frac{1}{2}$ to 4 drs or 2 to 16 grms

Manna is a mild laxative by virtue of its sugar. It is largely used for children and delicate women, in hot milk, or in combination with other purgatives.

L U ICINI

Castor Oil. (Ol. Ricin.)

Syn. I.V.—*Bheranda Tel*, Beng. *Arand Tel*, *Rendi Tel*, Hind.

Source —The oil expressed from the seeds of *Ricinus communis*.

Characters.—Viscid, nearly colourless, or faintly yellow. Odour, slight, taste, bland at first, acrid and unpleasant afterwards. Sp. gr. 0.958 to 0.969. **Solubility.**—1 in $3\frac{1}{2}$ of alcohol (90 p.c.).

Characters of the seeds.—Oval, compressed, shining marbled with reddish-brown or black-brown spots or stripes. Kernel white, albuminous, enclosing a large dicotyledonous leaf.

Composition.—The chief constituent is (1) *Ricinolein*, a mixture of glycerides of *ricinoleic* and *isoricinoleic acids*. (2) *Ricinoleic acid*, a viscid oil, believed to be the purgative principle. (3) *Glycerides of stearic and dihydroxystearic acid*.

B.P. Dose.—60 to 240 ms. or 4 to 16 mils.

PHARMACOLOGY

Externally.—Like almond oil and olive oil, castor oil is bland and unirritating. Rubbed into the skin, or injected into a vein or the rectum, it purges. It increases the secretion of milk when applied to the breasts, but poultices of the leaves of the castor oil plant are more effective.

Internally. Gastro-intestinal tract.—Its local action on the stomach is the same as on the skin, unless it is rancid when it causes nausea, eructations and vomiting. It acts by the formation of alkali ricinoleate as a result of saponification in the duodenum, which gently stimulates the intestinal glands and peristalsis, and is a painless, speedy, certain and fairly mild purgative operating within 2 to 6 hours. The stools are two to four in number, soft or semiliquid, but not watery, the oil being expelled with the last ones and occasionally causing griping. A portion of the oil is no doubt absorbed and when excreted by the mammary gland it may cause purgation to suckling babies. Some patients get habituated to its use, and in others it sets up after-constipation like rhubarb. X-ray examination after castor oil has shown that the colon becomes flaccid and does not recover its normal tone and mobility for two to three days. This possibly explains the cause of after-constipation.

THERAPEUTICS

Externally.—It may be used like olive or almond oil. A drop of castor oil let fall on the conjunctiva allays irritation caused by a foreign body. It is employed as a basis of many hair-oils and pomades.

Internally.—It is the safest and best **purgative** for children, the old and infirm, delicate females, women during and after pregnancy, and persons subject to piles and fissure of the anus. In abdominal operations, pelvic diseases, peritonitis, fevers, especially in the constipation of typhoid fever, castor oil is the safest purgative to be used. **Diarrhœa**, infantile or otherwise, caused by indigestible or undigested food, yields to a dose of castor oil with or without a minute dose of tinct. opii. It is an excellent remedy for **acute dysentery**, when given with opium which prevents griping, at the very onset.* Similarly in small doses (15 to 30 ms. with 5 to 10 ms. of tinct. opii emulsified) it is serviceable in the chronic variety. As an enema it has been given with success in impaction of the large intestine and rectum.

Dosage and mode of administration.—It has been observed that a minimum dose of 30 ms. and a maximum dose of 8 ozs. are required to open the bowels of an adult. As a rule it is rarely necessary to use more than 4 to 6 drs. for a single dose to an adult. Children can bear sometimes large doses. A small teaspoonful is not a large dose for a newborn babe. The disagreeable smell and greasy and sickening taste can be very well covered by emulsification with mucilage of acacia, or with yolk of eggs, or by giving in capsules. The oil must be warmed in cold weather, before administration. Taken floating on hot coffee, or half a teacup of warm water drunk two hours after a dose of the oil often helps its operation. Food retards or delays its action. A few drops of oil of turpentine mixed with the oil increases its purgative effect.

3. ANTHRACENE PURGATIVES

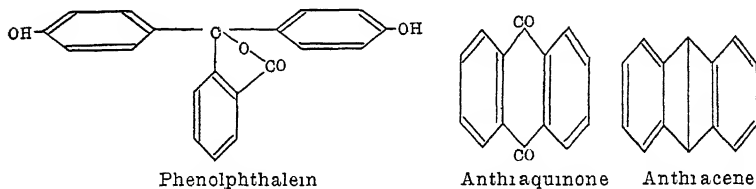
The drugs of this group—aloe, rhubarb, senna and cascara—owe their properties to the presence of *anthracene* ($C_{14}H_{10}$) derivatives of anthraquinone. All contain *emodin* or trioxymethylanthraquinone; rhubarb and senna also contain *chrysophanic acid* or dioxymethylanthraquinone,

*R

Ol ricini	ms 60-120
Bism carb	grs 7½
Tinct opii	ms 5-10
Mucil trag	qs
Syr aurant.	ms 60
Aqua menth pip.	oz 1

which colours the urine yellowish-brown. They have an excellent action, being neither too mild nor too strong a purgative. The synthetic preparation, phenolphthalein, has a similar composition and is considered under this heading. All these are valuable in habitual constipation, especially that of atonic type, but are not so good in spastic constipation, and in the presence of acid fermentation in the intestine there may be no cathartic effect. As a rule they do not act so well, or may fail in the absence of bile, but they may be made active by the addition of soap or an alkali. Their main action is on the large intestine, consequently they take about 10 to 15 hours to produce their effect. Since they act by increasing the contraction of the intestinal muscles they often cause griping and they are largely combined with belladonna, hyoscyamus or some volatile oil.

The constitutional formula of Phenolphthalein, Anthraquinone and Anthracene is given below:—



ALOE

Aloes. *N.O. Liliaceæ*

Syn. I.V.—*Musabar*, Beng., Hind.

Source.—The liquid, evaporated to dryness, which drains from the leaves cut from various species of *Aloe*. Known in commerce as Cape, Curacao, Socotrine, or Zanzibar aloes.

Characters.—Dark-brown or greenish-brown glassy masses; transparent in thin fragments (Cape aloes); or dark chocolate brown, opaque masses with a dull, waxy, uniform fracture (Curacao aloes); or hard, dark-brown, opaque masses with an uneven porous fracture (Socotrine aloes); or dark reddish-brown, opaque masses with a nearly smooth and slightly porous fracture (Zanzibar aloes); odour characteristic; taste, nauseous, bitter. *Solubility*.—Almost entirely in alcohol (60 p.c.).

Composition.—(1) A crystalline glycoside *Aloin* (Barbaloin). (2) *Aloe-emodin*, or trioxymethylantraquinone. (3) *Resin*. (4) *Volatile oil*, *gallic acid*, a trace.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Enters into.—Pil. Rhei Co, Pil. Colocynth. et Hyoscy., Tinct. Benzoin. Co., and the

OFFICIAL PREPARATIONS

1. *Pilula Aloes*.—B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.
2. *Pilula Aloes et Ferri*.—About $\frac{1}{2}$ gr. iron sulphate or $\frac{1}{4}$ gr. of iron in each 8 gr. pill. B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.
3. *Pilula Aloes et Asafœtidæ*.—B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.

ALOINUM

Aloin. (Aloin.)

Source.—A mixture of crystalline principles obtained from aloes.

Characters.—A pale yellow, microcrystalline powder; inodorous; taste, bitter. *Solubility.*—Almost entirely in water, in alcohol (90 p.c.).

Composition.—*Barbaloin* and *isobarbaloin* in equal proportions. Barbaloin is a *methyl-anthraquinone* derivative of a glycosidal character.

B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm

PHARMACOLOGY

Externally.—The activity of aloes is due to aloin. On the unbroken skin it has no action, but is absorbed from a denuded surface which it stimulates. If sprinkled over an ulcer, it causes purging.

Internally Gastro-intestinal canal.—In minute doses, aloes acts on the stomach as a stomachic, bitter tonic. It owes its property to the presence of glycosides of the anthraquinone derivative which are slowly hydrolysed in the intestine into irritant principles of the anthraquinone compound which act as purgative. Its action is not so marked on the small intestine, beyond slightly increasing the flow of bile, but it powerfully stimulates the muscular fibres of the colon, and slightly increases its glandular secretion. Therefore it is a cathartic, but its action is slow, taking 10 to 12 hours to purge. Large doses do not necessarily act earlier, but operate more violently and are accompanied by pain, griping, tenesmus and even bleeding from the rectum. In moderate doses the stools are soft, dark-coloured and formed and in large doses they are liquid. The slowness of its action is believed to be due to the fact that aloin cannot produce catharsis unless it is decomposed in the intestine into a more potent product by admixture with bile. Soap or alkalies combined with it help its solution, and to a certain extent prevent griping. The griping is caused by the irregular contractions of the colon. It increases the vascularity of the rectum, therefore the constant use of aloes may cause hæmorrhoids. When given as an enema it kills thread-worms. Aloin causes less griping.

Uterus—Aloin injected into animals stimulates uterine muscle, and its administration by the mouth is followed by increased contraction. Moreover by stimulating the pelvic circulation it causes congestion of the uterus. It is therefore an emmenagogue and may act as an abortifacient when given to pregnant women.

Elimination.—Emodin is excreted in large quantities with the milk, for suckling babies are purged when it is given to their mothers. Aloes is also eliminated to a slight extent with the urine.

THERAPEUTICS

Externally.—The Indian bazaar aloes (*musabar*) with turmeric or opium made into a paste is considered by the people of India as an effective remedy for contusions and swellings, but it remains to be proved how far it is beneficial in this respect.

Internally. **Gastro-intestinal tract.**—Aloes is reckoned as a valuable purgative in chronic and habitual constipation for it does not cause after-constipation, and gains instead of losing its activity by repetition. It is ordinarily given in the form of a pill with rhubarb, *nux vomica*, *ipécacuanha* or *colocynth*.* Its griping property is corrected by carminatives and extract of belladonna or *hyoscyamus*. An enema of aloes may be used as an anthelmintic.

Female diseases.—Because it causes pelvic congestion, aloes is given with success in amenorrhœa and delayed menstruation, especially when associated with dyspepsia and chronic constipation. When given with iron as *Pilula Aloes et Ferri*, it is very serviceable in anæmia, chlorosis and amenorrhœa of young girls.†

Caution.—Aloes is contra-indicated in pregnancy; irritable condition of the pelvic organs, especially rectum, hæmorrhoids, menorrhagia, and during the nursing period of mothers.

EU

Rhubarb

Syn.—*Rhei Rhizoma*; Turkey Rhubarb.

Source.—Rhizome of *Rheum palmatum*, and other species of *Rheum*, cultivated in China and Tibet deprived of most of its bark, and dried.

Characters.—In compact cylindrical, barrel-shaped, conical or planoconvex, or irregular pieces. The surface sometimes covered with a bright yellowish-brown powder. Rounded or angular, smooth, showing beneath dark red lines, intermixed with the reddish-brown substance of the root, usually presenting small scattered, star-like marks. Frequently the pieces are bored with a hole which sometimes contains the remains of the cord used to suspend them while drying. The root is hard and compact presenting a marbled, red and white appearance. Odour characteristic, aromatic. Taste, bitter, slightly astringent.

Composition.—(1) *Chrysophanic acid*, or dioxymethylantraquinone. (2) *Emodin*, or trioxymethylantraquinone. (3) *Rhein*, and (4) *Rheo-tannic acid*. (5) Oxalate of lime, rheumatic acid, resin, starch, etc.

B.P. Dose—3 to 15 grs. or 0.2 to 1 grm.

*R

Aloin	gr. 4
Strych. hydrochlor	gr. ¼
Pulv ipecac	gr. 6
Ext. bellad. sicc	gr. 1½
Ext gent.	q s
Make into 20 pills.	

†R

<i>Pil. aloes et ferri</i>
<i>Pil. aloes et myrrh. a a gr. 2</i>
<i>Ext hyoscy sicc gr ¼</i>

OFFICIAL PREPARATIONS

1. *Pilula Rhei Composita*.—B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.
2. *Pulvis Rhei Compositus* *Syn*—*Gregory's Powder*.—15 grs. in 60 grs. B. P. Dose.—10 to 60 grs. or 0.6 to 4 grm.
3. *Tinctura Rhei Composita*.—10 p c. B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY

Internally. **Alimentary canal**—Rhubarb tinges the saliva and increases its flow. In small doses (2 to 5 grs.), it stimulates the secretion of the gastric juice and the peristalsis of the stomach. It is therefore a **stomachic** and **tonic**. In the intestine, it performs two definite functions. (1) In large doses (20 to 30 grs.), it increases the secretion of the intestinal glands and the peristaltic movements, and thus acts as a **mild purgative**. This is due to chrysophanic acid and emodin, both anthraquinone derivatives. Purging occurs within 4 to 8 hours and is often accompanied by griping, and the stool is liquid and yellow, the colour being derived from the excess of bile and chrysarobin, the pigment. (2) After opening the bowels, the rheo-tannic acid constipates by arresting the glandular secretion of the intestine. This **astringent** action may also be produced by small doses of the drug, but the action of rheo-tannic acid is slower than that of chrysarobin.

Elimination.—Chrysarobin has been found in the milk, and largely in the urine, both of which are coloured by it. Large doses may even lead to irritation of the kidney. It makes the milk bitter and purgative. Rheo-tannic acid is excreted by the bowels.

THERAPEUTICS

Internally.—Rhubarb is largely employed as a stomachic and laxative in infantile ailments. It is an excellent remedy for the dyspepsia of children, especially when caused by a faulty diet. It expels undigested food, and produces first a soothing and afterwards an astringent effect. Goodeve's Red Mixture (*see* p. 104) is largely employed for this purpose in this country. In fact, it is one of our every day nursery remedies. Similarly, it is most effective in controlling infantile diarrhoea, produced by undigested food, or other irritating matter; here we look for the after astringent effect. Gregory's powder, which may be administered with milk, is a very useful aperient in many gastric and abdominal troubles of children.* As a pure purgative it cannot be pres-

*R

Hydrarg c. cret.	gr 1/8
Pulv. rhei co.	gr 2
Sod. bicarb	gr 2

cribed alone, on account of its griping and after-constipating properties, but combined with an equal quantity of soda, or with other purgatives, as pil. rhei co., it may be given for this purpose.† A full dose of Gregory's powder often cuts short an attack of mucous diarrhœa or dysentery, if given at the onset.

✓ **SENNAE FOLIUM**

Senna Leaf. (Senn. Fol.)

Source.—Consists of dried leaflets of *Cassia acutifolia* (Alexandrian senna), and of *Cassia angustifolia* (Tinnevely senna).

Characters.—Pale greyish-green or yellowish-green, thin brittle; 20 to 50 mm. long and 5 to 16 mm. wide, lanceolate or ovate-lanceolate; unequal at the base with entire acute lamina; distinct veins on the under surface; scattered hairs on both surfaces. Odour, slight; taste, mucilaginous, slightly bitter, and characteristic.

Composition.—The composition is not well known. Contains four glycosides (1) *rhein*, (2) *aloe-emodin*, (3) *kæmpferol*, and (4) *isorhamnetin*, (5) Anthraglucosennin, a mixture of several substances, (6) Cathartic acid.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

OFFICIAL PREPARATIONS

1. Confectio Sennæ.—10 p.c. B.P. Dose.—60 to 120 grs. or 4 to 8 grm.
2. ✓ Pulvis Glycyrrhizæ Compositus.—Senna 16 p.c. B.P. Dose.—60 to 120 grs. or 4 to 8 grm.

S ENNAE F UCTUS

Senna Fruit. (Senn. Fruct.)

Syn.—Senna Pod.

Source.—The dried ripe fruits of *Cassia acutifolia* (Alexandrian senna pods), and of *Cassia angustifolia* (Tinnevely senna pods).

Characters.—Alexandrian fruit, pale green with a brown central area; flat and thin, broadly oblong or somewhat reniform; 4 to 6 cm. long and up to 2.5 cm. wide; rounded at the apex, base sometimes ending in a short stalk. Pericarp, dry membranous, with about 6 flattened, obovate-cuneate seeds. Odour and taste, slight.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm. (4 to 12 pods).

OFFICIAL PREPARATIONS

1. Extractum Sennæ Liquidum—B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.
2. Syrupus Sennæ.—25 p.c. B.P. Dose.—30 to 120 ms or 2 to 8 mils.
3. Infusum Sennæ Concentratum.—B.P. Dose.—30 to 120 ms. or 2 to 8 mils.
4. Infusum Sennæ Recens.—B.P. Dose.— $\frac{1}{2}$ to 2 oz. or 15 to 60 mils.
5. Mistura Sennæ Composita. Syn.—*Black Draught*.—B.P. Dose.—1 to 2 oz. or 30 to 60 mils.

†R

Pil rhei co

Pil. hydrarg. a a gr 2

Ext. hyoscy. sicc gr. $\frac{1}{4}$

At bedtime to be followed in the morning by a saline

PHARMACOLOGY

Senna is a **laxative** or brisk **purgative** according to the dose used. The anthraquinone derivatives stimulate both the secretion and peristaltic action of the intestines, almost entirely the large intestine, and produce pale yellow watery stools containing some undigested food. It is not a cholagogue. Large doses cause griping. It possesses none of the tonic effects of rhubarb; on the other hand, purgation by senna does not cause subsequent constipation. It may however cause the urine, if alkaline, to be red. Injected into the veins, it causes vomiting and purging. It is eliminated with all the secretions and will purge the child when given to nursing women.

THERAPEUTICS

Senna is a safe purgative in slight cases of simple constipation and faecal accumulation, but, on account of its tendency to gripe and nauseous taste, it is rarely given alone.

It is largely used *to complete the effect of duodenal purgatives* in the form of a blue pill at bedtime and black draught in the morning. The compound liquorice powder is to be preferred to the black draught, as it is a very nasty mixture. The compound liquorice powder is largely used in habitual constipation and the constipation of pregnancy. Since senna causes pelvic congestion it should be avoided in hæmorrhoids and menorrhagia.

Prescribing hints.—The griping property of the black draught may be prevented by adding a few minims of tincture hyoscyamus. In the form of compound liquorice powder senna is largely used as a safe mild purgative. Infusion of senna pods is more active and causes less griping, and is very useful in cases of habitual constipation. Six to eight pods form the usual dose.

CASCA A SAG A A

Cascara Sagrada (Casc. Sagr)

Syn.—Rhamni Purshiani Cortex; Sacred Bark.

Source.—The dried bark of *Rhamnus Purshiana* (California buck-thorn).

Characters.—In quilled, channelled, or nearly flat pieces. 1 to 4 mm. thick, 10 to 20 cm. in length. Cork smooth, purplish-brown, almost covered with patches of silvery-grey lichens. Inner surface reddish-brown, longitudinally striated. Odour characteristic. Taste, nauseous, bitter and persistent.

Composition.—(1) *Emodin*, and (2) an allied substance possibly identical with *Frangula-emodin*. Also contains fat (2 p.c.), glucose, etc., *volatile oil*.

B.P. Dose.—20 to 60 grs. or 1·2 to 4 grm.

OFFICIAL PREPARATIONS

1. *Extractum Cascaræ Sagradæ Siccum*.—B.P. Dose.—2 to 8 grs. or 0·12 to 0·5 grm.
2. *Extractum Cascaræ Sagradæ Liquidum*.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
3. *Elixir Cascaræ Sagradæ*.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY

In small doses (5 to 10 ms.) of the liquid extract, cascara has a tonic effect on the stomach, promoting appetite and helping digestion. In moderate doses (30 to 60 ms.) it gently stimulates glandular secretion, but its action is upon the peristaltic movements of the large bowels. Hence it is a laxative, producing healthy, copious and bilious stools in 8 to 12 hours. In large doses it is a gastro-intestinal irritant.

THERAPEUTICS

Cascara is the most valuable aperient we have for habitual constipation. The dose ought to be so regulated as to produce a soft, painless, natural motion every morning, and when the desired end is gained, it should then be gradually reduced. The great advantage of the drug is that the dose does not require to be increased to maintain its action. However, for the successful cure of constipation it must be continued for at least 2 or 3 months.

Prescribing hints—The dry extract is best given in pills either alone or with *nux vomica* and aloes. The nauseous taste of the liquid extract may be concealed by aromatics and glycerin or aromatics and chloroform. The plain aromatic syrup is not an unpleasant vehicle. The elixir is a pleasant preparation. The uncertainty of its action is sometimes most annoying to the physician. This chiefly arises from the use by the manufacturers of inferior bark or the bark of allied species.

P N L P T A L I N U M

Phenolphthalein (Phenolphthal.). $C_{20}H_{14}O_4$

Syn.—Purgen.

Source.—Obtained by heating phenol with phthalic anhydride and sulphuric acid, and purifying the product.

Characters—A white, or yellowish-white, crystalline or amorphous powder, soluble in alcohol (95 p.c.), almost insoluble in water. No odour, no taste.

B.P. Dose.—1 to 5 grs. or 0·06 to 0·3 grm.

NON-OFFICIAL PREPARATION

1. *Tab Phenolphthaleini Co, B P C*—Each contains phenolphthalein 1 gr., ext belladonna sicc $\frac{1}{100}$ gr, strychnine sulphate $\frac{1}{500}$ gr. In habitual constipation. *Dose*—1 to 5 tablets

ACTION AND USES

Phenolphthalein in neutral solution is absolutely colourless, but on the faintest trace of alkali it turns delicate pink.

Under the name of "*Purgen*" it has been introduced as a purgative, being specially useful in cases where prompt action is required. It is dissolved by the bile or alkali and produces a mild irritant action in the small intestine, but powerfully irritates the colon, producing loose motions in from 6 to 12 hours without any griping. For ordinary patients $\frac{1}{2}$ to 3 grs. is a sufficient dose, but patients confined to bed may require as much as 10 grs. Part of the drug is absorbed and re-excreted in the bile and thus keeps up its action for several days. It has no action on the kidneys, but a small amount is excreted in the urine which it colours pink if alkaline. It is very safe and efficient in its action, but its use is contra-indicated in cases where there is a tendency to piles. It sometimes causes a rash in susceptible persons. Tetra-chlor-phenolphthalein given hypodermically (0.4 grm. in neutral olive oil 20 c.c.) is excreted by the bile and re-absorbed from the intestine and acts as a purgative.

The bromine and iodine compounds of phenolphthalein (Bromo-ray and Iodo-ray) are moderately opaque to X-ray and are used to take photographs of the gall-bladder.

4. DRASTIC PURGATIVES

IP OEA

Ipomœa. (*Ipom.*)

Syn.—Mexican Scammony Root. Orizaba Jalap Root.

Source.—Dried root of *Ipomœa orizabensis*.

Characters.—In irregular, tough or fibrous pieces, of varying size and shape; often in portions, 3 to 5 cm. wide and 2 to 4 cm. thick, which are transverse slices of large roots. Externally dark greyish-brown and wrinkled, internally greyish or brownish. Slight odour; taste, faintly acid.

B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 grm.

SCAI . NIA SINA

Scammony Resin. (*Scammon. Res.*)

Syn.—Resin of *Ipomœa*.

Source.—A mixture of resins obtained from *Ipomœa*.

Characters.—Brownish, translucent pieces, brittle. Fracture resinous. Odour, characteristic, fragrant. Does not form an emulsion with water. Soluble in alcohol (90 p.c.) and in ether.

B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm.

PHARMACOLOGY

Scammony or scammony resin acts like jalap. Its action begins only when it mixes with the bile in the duodenum. It is the taurocholate and glycocholate of soda of the bile that help its activity. It powerfully stimulates (a) the secretion of the intestinal glands, and (b) the muscular coat, though the contraction is irregular. As a result, free purgation occurs with griping in about four hours; the stool is first soft, but

soon becomes thin and watery. It is therefore a smart hydragogue purgative. It does not purge when injected into the blood, hence its action is entirely a local one. In large doses it causes gastro-enteritis

THERAPEUTICS

Internally —Scammony or scammony resin is rarely used alone on account of its griping qualities. By combining it with other purgatives, its own severity of action is mitigated, while the action of others is promoted. It acts promptly when given with an alkali; soap answering well. In severe constipation or impaction of feces the powder can be given with advantage, care being taken that there is no gastrointestinal irritation.

On account of its hydragogue properties it can be given in cases where depletion is necessary, as in apoplexy or cerebral congestion or where some effused fluid is to be absorbed, as in dropsy. Jalap answers better in such cases.

It can be used for the expulsion of intestinal worms after a dose of santonin and to complete the effect of vermifuges for round and tape-worms.

JALAPA

Jalap. (Jalap.)

Source.—The dried tubercles of *Ipomœa purga*.

Characters.—Dark brown; oblong, napiform or fusiform; 3 to 15 cm. long; larger ones incised; hard, compact, and heavy. Externally furrowed, wrinkled with small transverse scars. Internally yellowish-grey to dingy brown. Transverse section shows irregular, dark concentric lines. Odour, characteristic. Taste, sweet at first, acrid and disagreeable afterwards.

Composition.—(1) *Resin* 9 to 18 p.c., it appears to be identical with the resin obtained from scammony root. (2) *Jalapin* 10 p.c. insoluble in ether, also termed *Convolvulin* and *Jalapurgin*.

OFFICIAL PREPARATIONS

1. **Jalapa Pulverata.** *Syn.*—*Pulvis Jalapæ*.—Jalap reduced to a fine powder, adjust, if necessary, with suitable quantity of exhausted powdered jalap, or powdered lactose, to contain 10 p.c. of resin. B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 gm.

2. **Pulvis Jalapæ Compositus.**—30 p.c. B.P. Dose.—10 to 60 grs. or 0.6 to 4 gm.

PHARMACOLOGY

Jalap closely resembles scammony in action with this difference, that (1) it is less irritant and contracts less violently the intestinal muscular fibres, and therefore causes less griping; and (2) it produces a greater stimulation of the intestinal glands, and is therefore more hydragogue. It does not purge unless in contact with the bile. *Small doses* have a laxative effect. but large ones produce several watery

stools attended with pain and griping. Its action is entirely local, for it does not purge when subcutaneously injected.

THERAPEUTICS

Being a hydragogue purgative. Pulv. Jalap. Co. is employed in drawing off water in dropsy, ascites, and anasarca from whatever cause they may arise. It is also used in obstinate constipation, and is a revulsant in congestion of the brain, apoplexy, and engorgement of the right heart. Jalap is an excellent purgative in Bright's disease and uræmia. The resin in small doses can be given in habitual constipation. It should not be prescribed where the bowels are inflamed or liable to inflammation.

OLEUM CROTONIS (*Not official*) *Syn*—Oleum Tigli. The oil expressed from the seeds of *Croton Tiglium*. Brownish-yellow to dark reddish-brown viscid oil, odour, disagreeable. Taste, acid, burning. Contains (1) *Croton* resin, a powerfully vesicant substance, appears to be the active principle (2) Glycerides of stearic, palmitic, lauric, valeric, oleic, linolic and tiglic acids.

Dose— $\frac{1}{2}$ to 1 m. or 0.03 to 0.06 ml.

Identification of seeds—The seeds are oval or oblong, dark brown, marked with ramification of the raphe. They resemble castor-oil seeds, which are brighter, polished and mottled.

ACTION AND USES

It is a powerful irritant to the skin. When taken internally undiluted it irritates the mouth and fauces, followed by griping and abdominal pain and within an hour or two by repeated purging. It is a drastic purgative. It is used only when the patient is unconscious as in *cerebral hæmorrhage, coma* and in insanity on account of the minute dose and rapid and complete evacuation of bowels which follows. It is best given in pills, or mixed with butter or honey and placed at the back of the tongue.

COLOCYNT IS

Colocynth. (Colocynth.)

Syn.—Colocynthis Pulpa; Bitter Apple. *Syn.* I.V.—*Makhal phal*, Beng. *Indrabaruni*, Sans.

Source.—The dried pulp of the fruit of *Citrullus Colocynthis*. Contains not more than 5 p.c. of the seeds and 2 p.c. of outer sclerenchymatous part of the pericarp.

Characters.—White, spongy, light fragments. The powdered pulp exhibits abundant debris of large, thin-walled parenchymatous cells but no starch. No odour. Taste, bitter.

Composition.—(1) *Colocynthin*, a bitter amorphous purgative resin. (2) An amorphous purgative alkaloid, *colocynthinine*. (3) *Mucilage* and *gummy matter*.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

OFFICIAL PREPARATIONS

1. *Extractum Colocynthis Compositum.*—*B.P. Dose.*—2 to 8 grs. or 0.12 to 0.5 grm.

2. *Pilula Colocynthis et Hyoscyami.*—12.5 p.c. *B.P. Dose.*—4 to 8 grs. or 0.25 to 0.5 grm.

PHARMACOLOGY

Internally.—In minute doses colocynth is a bitter tonic. In moderate doses it stimulates the intestinal glands and the

muscles causing watery evacuations and griping. Hence it is a hydragogue drastic purgative. These effects may be produced if the drug is given either by the mouth or hypodermically, or injected into the circulation. In large doses these actions are aggravated and there is an intense gastro-intestinal irritation, reflexly affecting other abdominal and pelvic organs. It may therefore cause abortion.

THERAPEUTICS

Internally.—It is rarely prescribed for its tonic virtue, but is often given in combination with aloes and mercury in constipation due to hepatic disorder. It is an excellent purgative to relieve portal engorgement. It should always be given with hyoscyamus or belladonna to prevent griping. Hence pil. colocynth. et hyoscyami is a valuable preparation. Because of the watery character of the stools, it may sometimes be given in ascites, dropsy or cerebral congestion, but scammony and jalap are more powerful in this respect.

Caution.—It should not be given either to pregnant women or to persons who are subject to diarrhœa, dysentery, piles or gastro-intestinal congestion.

5 CHOLAGOGUE PURGATIVES

P P YLLU

Podophyllum. (Podoph.)

Syn.—Podophyllum Root; Podophylli Rhizoma.

Source.—The dried rhizome and root of *Podophyllum peltatum*, American May apple or Mandrake.

Characters.—Nearly sub-cylindrical, about 5 mm. thick; externally dark reddish-brown, smooth, or slightly wrinkled cylindrical pieces; presenting at intervals enlargements, which are marked on the upper surface by a depressed circular scar, and on the under surface stout, brittle rootlets, or their scars. Fracture short. Internally white, starch-like, or pale yellowish-brown and horny. Odour, characteristic. Taste, bitter, acrid.

Composition.—It is composed of (1) a neutral crystalline substance, *Podophyllotoxin* (0.2 to 1 p.c.), and (2) *Podophylloresin*, an amorphous resin, both of which are purgative (3) *Picropodophyllin*, quercetin and starch.

B.P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm

P P YLLU IN ICU

Indian Podophyllum. (Podoph. Ind.)

Syn.—Podophylli Indici Rhizoma

Source.—The dried rhizome and roots of *Podophyllum emodi*.

Characters.—Irregular and tortuous; knotty, 2 to 4 cm. long, and 1 to 2 cm. thick, flattened dorsiventrally. 3 to 4 cup-shaped scars on the upper surface; numerous root scars or stout roots on the under surface. Yellowish-brown to earthy-brown externally, fracture, short, internally pale brown and starchy and horny surface. Odour, slight, characteristic; taste, somewhat bitter and acrid.

B.P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

OFFICIAL PREPARATION

1. *Podophylli Resina* *Syn*—*Podophyllin*; *Vegetable Calomel*.—A mixture of resins, obtained from *Podophyllum*, or from Indian *Podophyllum*. Pale yellow to yellowish brown amorphous powder, or brownish-grey masses, turns darker on exposure to light or heat. Characteristic odour, with bitter, acrid taste. B.P. Dose.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 gm.

PHARMACOLOGY

Externally.—The resin acts as an irritant to the unbroken skin. The dust coming in contact with the eyes causes conjunctivitis. It is absorbed from raw surfaces and produces its specific effects, *i.e.* purgation.

Internally. *Gastro-intestinal tract*.—Being bitter and acrid in taste, podophyllin may excite salivation. It is a powerful hydragogue purgative. In purgative doses it causes griping, perhaps nausea, and within 10 to 12 hours a free watery stool. Much of the force of the drug is directed to the small intestine, more specially the duodenum, whose contents it sweeps along rapidly, in which respect it resembles calomel. Hence it has received the name of “vegetable calomel.” Beyond this it has none of the other properties of calomel. Impure resin produces more griping and common salt increases its cathartic effect. In large doses it gives rise to gastro-intestinal irritation. Bile dissolves the drug. As a purgative its action varies with different individuals, some being more susceptible than others.

Liver.—The bile found in the fæces after the use of this drug is due to diminished absorption owing to more rapid peristalsis not giving time for such absorption. It is an indirect cholagogue.

THERAPEUTICS

Internally.—As a purgative it is an excellent remedy for constipation, due to hepatic disorder or otherwise; the griping being corrected by hyoscyamus, belladonna, or cannabis indica. Its action becomes more uniform and certain when combined with other purgatives, *e.g.* aloes, jalap, colocynth, rhubarb.* Calomel and podophyllin make a very advantageous combination, as they aid each other's action on the same portion of the intestine. Being an indirect cholagogue it is best suited for constipation caused by the torpid condition of the liver, biliousness or hepatic dyspepsia. $\frac{1}{8}$ to $\frac{1}{4}$ gr. can be recommended as an ordinary dose for habitual constipation, but $\frac{1}{4}$ to $\frac{1}{2}$ gr. should be given in

*R

Podoph res	gr. $\frac{1}{8}$
Pulv ipecac	gr. $\frac{1}{8}$
Ext euonym	gr. 1
Ext nuc. vom sicc	gr. $\frac{1}{8}$
Ext. hyoscy. sicc.	gr. $\frac{1}{2}$
Pil rhei co.	gr 2

Pill for habitual constipation with torpid liver

obstinate constipation or to relieve portal congestion. Sometimes larger doses are necessary. Whey, sherbet or mucilaginous drinks stop excessive purging.

It is given in non-purgative doses ($\frac{1}{30}$ to $\frac{1}{20}$ gr.) in many functional disorders of the liver, characterised by metallic taste in the mouth, dull depressed spirits, sluggish bowels, sick headache, etc.

IRIDIN (*Not official*). *Syn*—Extractum Iridis B.P.C.—An extract obtained from the root of *Iris versicolor*, the Blue Flag. A dark brown resinous powder, having a bitter acrid taste.

Dose—1 to 3 grs. or 0.06 to 0.2 gm.

PHARMACOLOGY AND THERAPEUTICS

Iridin is used in biliousness and all sluggish conditions of the liver. It should be administered in the form of a pill made up with glycerin of tragacanth or extract of hyoscyamus. It may be usefully combined with euonymin and podophyllin.

EUONYMUS (*Not official*).—The dried root-bark of *Euonymus atropurpureus*. Contains (1) A bitter crystalline alcohol *euonymol*, (2) the sterols, euonysterol atropurpurool, and a mixture of fatty acids.

NON-OFFICIAL PREPARATIONS

1 **Extractum Euonymi**, B.P.C. *Syn*.—*Euonymin*.—*Dose*—1 to 2 grs. or 0.06 to 0.12 gm.

2 **Tinctura Euonymi**, B.P.C.—Bark 4, alcohol (45 p.c.) *q.s.* to 20. *Dose*—10 to 40 ms. or 0.6 to 2.6 ml.

3 **Liquor Euonymini et Iridini**, B.P.C.—Ext. euonymus 320 grs., ext. iridis 160 grs., pot. carbonas 120 grs., water 5 oz., alcohol (45 p.c.) *q.s.* to 20 oz. *Dose*—30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

The action of euonymin resembles in many respects that of podophyllin, but is milder. It is a very useful remedy in hepatic disorders, and in constipation, especially when it is due to torpidity of the liver. Combined with cascara, it may be given with very good results in chronic or habitual constipation. The following powder is very useful in infantile hepatic enlargement with slow fever.*

GROUP X

DRUGS ACTING ON THE LIVER

The liver is by far the largest gland in the body and plays an important part in the general metabolism. Any derangement of its functions upsets the whole metabolic balance and produces diverse symptoms. It performs the following important functions:—(1) Formation of bile, which is partly secretory and partly excretory. It forms the bile pigment from the hæmoglobin which is excretory, and any disturbance of its function is characterised by jaundice, due to failure of the organ to excrete bilirubin. These pigments take

*R

Ext. euonym	gr. $\frac{1}{2}$
Pulv. ipecac	gr. $\frac{1}{8}$
Salicin	gr. 1
Pulv. rhei co.	gr. 2
Sod. bicarb.	gr. 2

no part in the digestive process but get mixed with the food in its passage through the intestine where, they are broken up by the bacterial activity. The bile acids are secretory and help in the absorption of fats. These acids, or their products of decomposition, are partly absorbed from the intestine and are re-excreted by the liver. In the liver they stimulate the secretory cells and act as *natural cholagogues*. (2) Plays an important part in iron metabolism by conserving organic iron and forming hæmoglobin. It produces the anti-anæmic factor by the interaction between the intrinsic factor in the gastric juice and the extrinsic factor in protein food which is essential for the development of megaloblasts into normoblasts and reticulocytes in the bone-marrow. It is also supposed to help normal coagulation of the blood by forming fibrinogen. (3) Regulation of carbohydrate metabolism. By removing the excess of sugar from the portal blood and storing the excess as glycogen it maintains the concentration of sugar in the blood at a constant level of 0.12 p.c. In this function it is helped by the hormones of the pancreas, the adrenal medulla, the thyroid, and the pituitary gland. (4) Regulation of protein metabolism. It helps to metabolise amino-acids which are absorbed from the intestine as the end products of protein digestion. The ammonia salts formed as the result of protein digestion are converted into harmless urea. (5) Protects the body from the action of toxins either produced during metabolism or absorbed from the intestine. They are either excreted unchanged in the bile, or may be broken down or synthesised into harmless compounds, or may be stored in the organ to be excreted slowly. Many drugs and toxic substances are excreted by the bile. Iodophthalein (see page 366) when given intravenously or administered *per os* is excreted into the gall-bladder rendering it opaque to X-ray. (6) Regulation of uric acid metabolism. This is not of much value in man.

Drugs that influence the secretion of bile.—Drugs that increase the secretion of bile are known as cholagogues. They may be direct and indirect. Bile is being continually secreted by the liver, and the gall-bladder acts as a storage reservoir, and ejects it intermittently into the intestine during digestion. Normally the entrance of the chyme into the duodenum is followed by contraction of the gall-bladder and this has been attributed to a hormone *cholecystokinin* formed in the duodenum by the entrance of acid chyme from the stomach. If the meal contains an excess of fat and protein or their products of digestion, the contraction is more powerful. The formation of secretin has also a stimulating effect both on the contraction of the gall-bladder and on the formation of bile. It does not mean that simply because more bile appears in the stool there is an increased secretion of bile; either the gall-bladder or the ducts have emptied more thoroughly, or the bile poured into the duodenum has been swept down without giving time for reabsorption.

Direct Cholagogues.—These are also called cholaretics. By far the best cholagogues are bile and bile salts, then come the salicylates and benzoates, soap and dilute hydrochloric acid. Mellanby has shown that secretin entering the blood stream excites the pancreatic secretion and bile, and any substance that helps the formation of secretin will increase secretion of bile.

Indirect Cholagogues.—These cause the bile to be rapidly swept along the intestine without allowing time for its reabsorption. They act by stimulating contraction of the gall bladder. Fats, yolk of egg, olive oil, and castor oil accelerate emptying of the gall-bladder. Similarly magnesium sulphate hypertonic solution (33 p.c.) helps expulsion of bile. The following drugs have a reputation of being indirect cholagogues, viz. podophyllum, euonymus, iridin, ipecacuanha, mercurials, colchicum, rhubarb, ammonium chloride, and histamine.

Drugs used to dissolve gall-stones are called biliary lithontriptics

—Inflammation of the gall-bladder or cholecystitis is a common affection and is often due to some bacterial infection. The chief organisms responsible are *B. coli*, *streptococcus*, and *B. typhosus* or *B. paratyphosus*. It may also result as an extension of inflammation from the duodenum. This is often associated with gall-stones. Several drugs have been used in cholecystitis, the most commonly used drug is hexamine (*q.v.*). In some cases specific vaccine gives good result. The treatment of gall-stones by drugs is very unsatisfactory. The following are used to expel, reduce or dissolve the stones, viz. sodium salicylate and aspirin make the bile watery, olive oil, etc.

Glycogenic function of the liver is stimulated by adrenaline, pituitrin and thyroxine which cause glycosuria by converting glycogen into glucose. Antimony, arsenic, phosphorus and opium depress the function

Class A : Chologogues

EXT ACTUM F LLIS OVINI

Extract of Ox Bile. (Ext. Fell. Bov)

Syn —Fel Bovinum Purificatum.

Source —Obtained by evaporating fresh ox bile to one-fourth of its volume, shaking it with alcohol (90 p.c.), filtering and evaporating the residue to the consistence of a firm extract. Contains the bile salts and pigments, free from mucus

Characters.—A dark yellowish-green, plastic substance, taste, bitter and disagreeable. *Soluble* in water, and in alcohol (90 p.c.)

B.P. Dose —5 to 15 grs or 0.3 to 1 grm.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Bile is bitter, but cannot replace vegetable bitters as a stomachic. Given by the mouth most of it is absorbed in the intestine and carried to the liver which excretes it again, a small quantity of the bile acids being eliminated with the urine. It is a valuable chologogue, and increases the secretion of both the solids and the fluids of the bile. The bile acids irritate the mucous membrane of the colon and act in the absence of bile. Bile increases the lipolytic ferment of the pancreas and helps the absorption of fats, and is therefore used in those cases of dyspepsia and constipation in which the natural secretion of bile is very deficient. 20 to 30 grs. of bile extract dissolved in 1 or 2 ozs. of water may be given as a clyster in cases of impaction of fæces in the rectum, where there is no room for a larger enema. It is generally given in cachets or in solution, but it is best administered in the form of keratin-coated or salol-varnished pills, two hours after food.

Class B : Drugs used for Diagnostic Purposes

- 1 For X-ray examination of the alimentary canal.
Barium Sulphate (*see* page 107), Bismuth Subnitrate (*q.v.*)
- 2 For X-ray examination of the gall-bladder
Iodophthalein
3. For testing liver function
Lævulose (*q.v.*)

IO OP T ALEINUM

Iodophthalein. (Iodophthal.). $C_{20}H_8O_4I_1Na_3 \cdot 3H_2O$

Syn.—Iodo-ray. Opacin

Source.—Di-sodium salt of tetraiodophenolphthalein Prepared by the iodination of phenolphthalein. Contains not less than 85 p.c of phthalein The separated phthalein contains 61 to 62 p.c of iodine.

Characters.—A blue or blue-violet, crystalline powder. Odourless; taste, saline, astringent Soluble in 7 parts of water. Slightly soluble in alcohol (90 p.c)

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{4}$ gr. per pound of body weight up to 75 grs. or 0.04 to 0.06 grm per kilogramme of body weight up to 5 grms. For *intravenous injection* up to 45 grs or up to 3 grms.

USES

Given intravenously or *per os* it is excreted by the liver into the gall-bladder rendering it opaque to X-ray. Therefore it is largely used for diagnosis of cholecystic disease by **cholecystography**. For all practical purposes, oral use is sufficient, intravenous use is necessary only after negative results from oral use. The patient takes a light evening meal at 7 p.m., and at 10 p.m., two keratin coated gelatin capsules of 5 grs. each are taken followed by a drink of water. Every fifteen minutes two capsules are taken at a time till ten have been swallowed, accompanied by free drinks of water. In fact the patient should keep drinking water till he falls asleep. No food is given the following day. Examinations are made at 10 a.m., 11 a.m. and 4 p.m. At 5 p.m. the patient is given some bread and butter and another examination is made to see the effect of meal upon the shadow. For successful examination it is necessary that the drug must be absorbed and excreted by the liver, and that the hepatic and cystic ducts must be patent, as otherwise the gall-bladder will not fill. It is also important that the dye must freely enter and leave the liver.

Graham's technique for intravenous use is as follows:—The injection is given early in the morning, and no food is taken except a glass of milk if hungry, although water may be drunk during the day. Three grammes are dissolved in 40 c.c. of triple distilled water and half the amount is injected slowly taking 5 to 7 minutes; half an hour later the remaining half is injected. It is necessary to wash through the needle some normal saline.

Nausea and vomiting with fall of blood pressure may occur occasionally and should be counteracted by injection of 10 ms. of adrenaline solution. 40 grs. of bicarbonate of soda in solution should be taken every three hours, day and night, as long as the patient remains awake. Radiograms are taken 3 and 6 hours after the injection. The solution must be freshly prepared.

GROUP XI

ASTRINGENTS

Astringents form a special group of drugs whose action is characterised by contraction or shrinkage of the tissues and diminished exudation or secretion. In the intestine their effects are antagonistic to purgatives. They include the *astringent metals*, *acid sulphuric dilute*, and *vegetable astringents*. Opium and chalk act as intestinal astringents by diminishing the secretions and peristalsis.

The *vegetable astringents* owe their property to the presence of tannin. They precipitate proteins and form a blue or black compound with iron preparations. They are milder in their effects than the astringent metals, and being practically harmless they are specially used in diseases of the alimentary canal. All astringents are *local hæmostatics*, i.e. check bleeding by precipitating a hard coagulum which plugs the bleeding vessels (*see page 286*). They have no action on the vessel walls. Since astringents are precipitated by proteins they are not much absorbed, nor do they exist in the blood and tissues in sufficient quantity to be of any use. They have therefore no remote astringent effect and act only on the part on which they are applied.

Tannic acid or substances containing it form more or less insoluble compounds with many metals, alkaloids, glycosides, etc., and may therefore be used as their antidotes.

- Astringents are classified as follows :-

1. Metallic astringents *see page 118*.
2. Vegetable astringents

Tannic acid, Catechu, Rhatany, Hamamelis, Myrobalan (*q v.*)

ACIDUM TANNICUM

Tannic Acid. (Acid. Tann.)

Syn.—Tannin; Digallic Acid.

Source.—Obtained from the galls of various species of *Quercus*, by subjecting them to special fermentation and extracting them with water-saturated ether.

Characters.—Yellowish-white or light brownish, glistening scales, light masses, or an impalpable powder; odour, characteristic; taste, slightly astringent. *Soluble* in 1 part of water and alcohol (90 p.c.), freely in acetone, slowly in 1 part of glycerin. An aqueous solution forms precipitates in solutions of gelatin, albumen and some alkaloids.

B.P. Dose—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATIONS

1. Glycerinum Acidi Tannici.—15 p.c. B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.
2. Suppositorium Acidi Tannici.—3 grs. or 0.2 grm. in each.
3. Trochiscus Acidi Tannici.— $\frac{1}{2}$ gr. or 0.03 grm. in each.
4. Unguentum Acidi Tannici.—20 p.c.

NON-OFFICIAL PREPARATIONS

1. Acidum Acetyltannicum, U.S.P. *Syn*—*Di-Acetyl-tannin*; *Acetannin*: *Tannigen*—A product obtained by the acetylation of tannic acid. A yellowish or greyish-white powder. Darkens on exposure to light. Slightly soluble in water and in alcohol. In *enteritis* and *infantile diarrhoea*. *Dose*, U.S.P.—10 grs or 0.6 grm.

2. Albumini Tannas, U.S.P. *Syn*—*Albutannin*—A compound of albumin and tannic acid. A yellowish-white, odourless powder. Almost insoluble in water. *Dose*, U.S.P.—30 grs or 2 grm

3 **Tannoform.** *Syn*—*Methyl Ditannin*.—A condensation product of tannic acid and formaldehyde, in reddish-white powder insoluble in water. As a dusting powder in *hyperhidrosis*, *bed-sores*, *soft chancres*, *eczema*, etc. Internally in *infantile diarrhœa*. *Dose*.—8 to 15 grs. or 0.5 to 1 gm.

PHARMACOLOGY

Externally.—Tannic acid or substances containing it coagulate albumin, gelatin and mucus. Tannic acid has no action on the unbroken skin, but applied to an exposed mucous membrane or a denuded surface it coagulates the mucus and the albuminous secretions, and forms a firm insoluble protective covering over the part. The coagulated albumin or gelatin resists putrefaction. Absorbed into the tissues, it coagulates the interstitial fluids, and condenses the albuminous and connective tissues, and thereby diminishes the serous discharge. Hence it is a powerful local **astringent**. It arrests hæmorrhage partly by plugging the small vessels, and partly by the production of a coagulum in the surrounding tissues, but it has no action on the muscular coats. It is therefore a local **hæmostatic**. It slightly depresses the local sensory nerves, and has feeble antiseptic and irritant properties.

Internally. **Alimentary canal.**—Tannic acid causes dryness of the mouth with a feeling of astringency and of stiffness of the tongue and throat, owing to the coagulation of the secretions of the mucous membranes. These effects are due to the direct chemical effect on the protein. Its action on the stomach is the same as on the mouth. A portion of it is converted into tannate when it loses its astringent property till the tannate of albumin is redissolved in the gastric juice and tannin is again liberated. Pepsin and peptone are precipitated in a neutral solution, therefore they are not affected because of free acid, but large doses impair digestion by precipitating pepsin, and often cause gastric irritation and vomiting, but stop hæmorrhage by local hæmostatic property. In the intestine it causes constipation by precipitating proteins and diminishing the glandular secretions, thus making the stools harder and drier. It precipitates yeasts and microbes and acts as a mild antiseptic and renders the fæces less offensive by decreasing the number of bacteria. The undecomposed tannates and unabsorbed gallates are thrown off with the fæces. Tannic acid cannot affect the biliary secretion.

Blood.—Tannic acid enters the blood mostly as gallates and partly as tannates and circulates as such. Injected into a vein it causes death by thrombosis.

Elimination.—There is a great diversity of opinion as to its excretion. According to some, any that has been absorbed is decomposed in the human body, only about 1 p.c. is detected in the urine or fæces; although gallates and traces

of tannates are found in the urine of animals. But Stockman found gallic acid with traces of tannin in the urine when pure tannin was given by the mouth; and a large amount of tannin with a little gallic acid in the urine when sodium tannate was administered.

THERAPEUTICS

Externally.—As a *local hæmostatic*, tannic acid is largely employed in hæmorrhages from the nose, the rectum, the bladder, the urethra, etc. It may be used as a snuff or a nasal douche in epistaxis, or as an ointment or a suppository in hæmorrhoids. As a *local astringent*, it is useful in subduing mild forms of subacute or chronic inflammatory processes and discharge from the skin, as in eczema, intertrigo (*Glycerinum Acidi Tannici*); the ear in otorrhœa (*Glycerinum Acidi Tannici*); the eye, as in conjunctivitis and corneal vascularity (as collyrium 4 grs. to 1 oz.); the nose, as in ozæna (a douche, snuff or paint); the vagina, as in leucorrhœa (an injection, douche or pessary); the uterus, as in ulcerated os (pessary or cotton-wool soaked in tannic acid and glycerin); the bladder, as in cystitis (injection); and the rectum, as in ulcers, fissures and prolapse of the rectum (an injection or suppository).

It is valuable in the treatment of burns, when applied as a dressing with $2\frac{1}{2}$ p.c. freshly prepared solution and kept saturated till the area is tanned a mahogany brown. Recently it is used in 5 p.c. solution for children and 10 p.c. solution for adults. The value of this treatment depends upon the production of a tightly adherent rigid crust over the burnt surface. It diminishes pain, prevents fluid depletion, decreases toxæmia, and in the 2nd and 3rd degree of burns allows epithelisation to proceed while the membrane is in place. The great advantage of this treatment is the prevention of the absorption of toxin which generally causes death on the 2nd and 3rd day after the injury. When sprayed over the wound no dressing is applied and the spraying done every 15 minutes until a dry brown crust forms which seals the wound. There are however certain disadvantages of tannic acid, viz. its solution is unstable, it has no anti-septic power, and it is not isotonic. To obviate these disadvantages Barnard Fantus and H.A. Dyniewicz* recommend the following solution, viz. pot. chlor. 0.42 grm., cal. chlor. 0.84 grm., salicylic acid 1.00 grm., sod. chlor. 10.50 grm., tannic acid 100.00 grm., distilled water to 1000 c.c.

Internally. Alimentary canal.—Tannic acid makes a very good dentifrice for bleeding and ulcerated gums. Glycerin of tannic acid is a valuable application in ulcerative stomatitis, subacute or chronic sore-throat, relaxed or elongated

**Jour Amer Med. Assoc*, July 17, 1937

uvula, enlarged tonsils, etc. A gargle (glycer. acid. tann. 1 dr. to 1 oz.), a spray (1 dr. in rose water 10 ozs.), or lozenges may be used in these cases. An insufflation of tannin with starch makes an excellent application for the mouth and larynx. It is a valuable remedy for gastric and intestinal hæmorrhage, but it should be given in large doses, say 30 to 40 grs. every one or two hours. It is a valuable antidote in poisoning by alkaloids and antimonial salts. It is largely used in diarrhœa either acute or chronic, but preparations of catechu are generally preferred.

Prescribing hints.—Internally it may be given in solution, cachets, or pills. In the absence of tannic acid any vegetable infusion containing tannin, such as strong tea or decoction of oak bark, may be employed in alkaloidal poisoning. It should not be combined with ferric salts which it colours black; with mineral acids it precipitates tannin, and with alkalies it forms soluble tannates, but the solution changes colour becoming black. Caffeine is precipitated by tannic acid but is redissolved if the latter be in excess.

CAT C U

Catechu. (Catech.)

Syn—Pale Catechu; Gambir. **Syn. I.V**—*Khayer*, Beng, *Kath*, Hind.

Source.—A dried aqueous extract of the leaves and young shoots of *Uncaria Gambier*

Characters.—In cubes, sometimes agglutinated. Each side about 25 mm. Pale greyish-brown to dark, reddish-brown externally, pale brown internally, porous and friable. Taste, at first bitter and astringent, then sweetish. No odour. **Solubility**—Entirely in boiling water.

Composition—(1) *Catechu-tannic acid*, 22 to 50 p.c. (2) *Catechin* 7 to 33 p.c. (3) *Quercetin*, catechu-red, *gambier-fluorescein*, wax, oil, etc.

Incompatibles—Alkalies, metallic salts, gelatin.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

OFFICIAL PREPARATION

1. *Tinctura Catechu*—1 in 5. **B.P. Dose**—30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Catechu is a non-irritating astringent, acting like tannic acid, which it contains. It is a valuable *local astringent* and may be used in the form of dentifrice, gargle, paint, or lozenge for spongy gums, mercurial and ulcerative stomatitis and relaxed throat.* Catechu is a very useful remedy for diarrhœa and in the early stages of cholera, being often prescribed with opium and chalk.

*R

Tinct catech ms. 60
Glycer. alum. ad oz 1

K A M E I A

Krameria. (Kramer.)

Syn—Rhatany Root, *Krameria Radix*.

Source—The dried root of *Krameria triandra*, known as Peruvian Rhatany.

Characters—Nearly cylindrical, slightly flexuous, reddish-brown, 15 mm thick, cork, scaly with polygonal cells and dark-brown walls. Fracture, shortly fibrous in the bark, splintery in the wood, bark, bright reddish-brown, about one-third of the radius of the root in thickness. Wood, pale reddish-brown, finely radiated in transverse section. Odourless. Taste of bark astringent, wood nearly tasteless.

Composition—(1) *Rhatania-tannic acid*, 8.4 p.c. (2) Rhatania red, the colouring matter (3) Rhatannin, neutral substance.

Incompatibles.—Alkalies, lime water, iron, lead salts and gelatin.

B.P. Dose—10 to 30 grs. or 0.6 to 2 gm.

OFFICIAL PREPARATIONS

- 1 Extractum *Krameria* Siccum.—B.P. Dose—5 to 15 grs. or 0.3 to 1 gm.
- 2 Tinctura *Krameria*—B.P. Dose—30 to 60 ms. or 2 to 4 mls.
- 3 Trochiscus *Krameria* *Syn.*—*Krameria Lozenge*—1 gr. or 0.06 gm. in each
- 4 Trochiscus *Krameria* et Cocainæ *Syn.*—*Krameria and Cocaine Lozenge*.—1 gr. or 0.06 gm. of extract and $\frac{1}{20}$ gr. or 0.003 gm. cocaine hydrochloride in each

PHARMACOLOGY AND THERAPEUTICS

Internally.—Rhatany is a powerful astringent, because of the tannic acid it contains. The powdered root forms an important ingredient in many dentifrices and the tincture in mouth-washes. A teaspoonful of tincture in 1 oz. of water, or the infusion of the root, makes a good gargle in relaxed sore-throat, spongy and ulcerated gums and mercurial stomatitis. *Krameria* and cocaine lozenge is very efficacious in sore-throat.

A A M L I S

Hamamelis. (Hamam.)

Syn—Hamamelidis Folia; Witch Hazel Leaves.

Source—The fresh or dried leaves of *Hamamelis virginiana*.

Characters.—Broadly oval, 7 to 15 cm long, upper surface dark green or brownish-green, pale below, apex obtuse, base oblique, cordate and shortly petiolate, margin, sinuate, veins, pinnate and prominent on the under surface which is furnished with stellate hairs. Taste, astringent, slightly bitter. No odour.

Composition—(1) *Tannic acid*, (2) *Gallic acid*, a bitter principle, and a volatile oil.

OFFICIAL PREPARATION

1. Extractum *Hamamelidis* Liquidum—1 in 1 B.P. Dose—30 to 60 ms. or 2 to 4 mls

NON-OFFICIAL PREPARATION

- 1 Unguetum *Hamamelidis*, B.P.C.—Liquid extract of hamamelis, 10 p.c. in wool fat and yellow soft paraffin.

PHARMACOLOGY AND THERAPEUTICS

As a local astringent or hæmostatic it has been used in various ways and in various affections in place of tannic

acid. It may be used as a gargle in sore-throat, bleeding from the gums, ulcerative stomatitis, or as an injection in gonorrhœa, vesical hæmorrhage, nasal catarrh, epistaxis, etc. Hamamelis is a most valuable remedy for internal and external piles.

GROUP XII

ANTHELMINTICS

Anthelmintics are drugs which kill or expel intestinal worms. *Vermicides* are remedies which kill the worms, while *vermifuges* expel them without necessarily killing them. Active peristalsis tends to remove intestinal parasites with other intestinal contents. Thus drastic purgatives are sometimes used for the purpose of expelling the worms with partial benefit. Since the worms fix themselves with their hooks, suckers or serrated margins, they must be weakened or narcotised or killed before they can be effectively expelled.

An ideal anthelmintic is one whose value depends not only upon its poisonous effects upon the parasites in the intestinal canal, but also upon its harmlessness as regards the patient, *i.e.* the drug should exert its influence on the worms without being absorbed, and since it is desired to attack the worm rather than the host, the dose must be as large as can be borne by the patient without producing any toxic effect. Safe doses of the vermicides do not kill the parasites, but only depress or narcotise them, and these would recover if left in the intestine. It is therefore customary to follow the use of the vermicide with a purgative. This also prevents any absorption of the drug and so diminishes the toxicity. The choice of a preliminary purgative depends upon the nature of the anthelmintic used. Thus for drugs like male fern, thymol, carbon tetrachloride, purgative oils should be avoided, since oil helps absorption of these drugs. Whereas castor oil may be used with oil of chenopodium. It has the further advantage of counteracting the paralyzing action of oil of chenopodium on the intestine. Magnesium sulphate (half an ounce in water) is an all round good purgative. Calomel may also be used followed by magnesium. In large doses most anthelmintics act as gastro-intestinal irritants.

In cases of infection with tape-worm or hook-worm, the use of an anthelmintic is usually preceded by a fast so that the parasite will not be protected by the intestinal contents. This however has the disadvantage of weakening the patient and also helping absorption of the drug. In any case the fast should not be severe. In mass treatment it is a great disadvantage and its use is disappearing specially with weak and debilitated patients. After a light evening meal a dose of purgative is given and the anthelmintic is taken first thing in the following morning either in one dose, or in two or three divided doses given every hour, to be followed two hours after the last dose by another dose of the purgative. A preliminary saline purgative often helps to remove intestinal mucus and thus helps the exposure of the worms to the action of the anthelmintic. Magnesium sulphate or sodium sulphate or both may be used. Santonin is best given at bedtime on account of its effects on the retina.

A number of drugs belonging to other groups, for instance, oil of turpentine, beta-naphthol, thymol and chloroform also enjoy the reputation as anthelmintics.

Apart from the infection of the human gut with helminthes, many worms inhabit the tissues of the host and cause *somatic infections*. They are chiefly the different varieties of Bilharzia (*Schistosoma*) and Filaria, the former giving rise to the condition known as Bilharziasis and the latter Filariasis.

Antimony and *emetine* have been used in the treatment of Bilharziasis with some benefit. Emetine has also been used in infestation with *Fasciola hepatica* (Liver fluke) and *Paragonimus* (Lung fluke).

Filariasis has been treated with *arsenic* and *antimony* but the results were disappointing.

Anthelmintics are classified as follows :

Class A Anthelmintics for Round-worm

Santonin, Carbon Tetrachloride, Oil of Chenopodium, Butea Seeds (*q v*)

Class B Anthelmintics for Tape-worm

Male Fern, Pelletierine Tannate, Melon Pumpkin Seeds (*q v*)

Class C Anthelmintics for Hook-worm

Thymol (*q v*), Beta-naphthol (*q v*), Carbon Tetrachloride, Oil of Chenopodium, Tetrachlorethylene, Hexyl-resorcinol

Class D Anthelmintics for Thread-worm

Rectal injections of a solution of Common Salt, strong infusions of Quassia and Calumba, solutions of Ferric Salts and Decoction of Aloes, and Carbon Tetrachloride by mouth

CLASS A: Anthelmintics for Round-worm

SANTONINUM

Santonin. (Santonin.). $C_{15}H_{18}O_8$

Source.—A crystalline principle obtained from *santonica*, the dried unexpanded flower-heads of *Artemisia cina*, and other species of *Artemisia*.

Characters.—Colourless, flat, rhombic prisms, feebly bitter, turning yellow by sunlight. **Solubility.**—Almost insoluble in water, soluble in $2\frac{1}{2}$ parts of chloroform and in 50 parts of alcohol (90 p.c.).

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm. $\frac{1}{4}$ to $\frac{1}{2}$ gr for a child 1 year old; 1 to $1\frac{1}{2}$ grs for a child 2 to 5 years.

PHARMACOLOGY

Internally. Intestines.—Santonin is a direct poison to round-worms, *Ascaris lumbricoides*, killing them in the intestine. Its action is less marked on thread-worms, *Oxyuris vermicularis*, and it has no effect whatever on tape-worms. Some assert that it does not kill but paralyses the worm. In fact many worms are passed out alive. It is a valuable anthelmintic for round-worms, although it does not kill them outside the body. It is partially dissolved in the stomach and passes into the intestine where it acts as an anthelmintic. This effect is possibly due to an unknown oxidation product formed in the intestine. Sometimes a portion may be absorbed and though this may not give rise to any toxic symptoms there is yellow vision (xanthopsia) and colouration of the urine. In vermicidal doses it does not cause purgation, but does so when given in large quantities.

Absorption.—It is oxidised in the tissues and is excreted in the urine and faeces in the form of oxysantonins. After a therapeutic dose the entire quantity is eliminated by the urine as a coloured substance although traces of santonin may be detected in the urine after large doses.

Nervous system.—It produces some curious effect here.

Even in medicinal doses, within an hour or two after administration, objects first appear bluish, and then greenish or yellow, due perhaps to a certain disturbance of the retinal fibres, for though there is hyperæmia of the retina, yet the humours and other tissues of the eye are not stained. Taste and smell are sometimes affected.

Kidneys.—Santonin is chiefly excreted by the kidneys, and during its passage increases their secretion. Sometimes it may create dysuria or incontinence of urine in children. It colours acid urine greenish-yellow and alkaline urine purplish-red, referable probably to an unknown oxidation product formed in the system and excreted with the urine.

Toxic action.—In large doses it causes headache, vomiting, purging, loss of consciousness and speech, cold sweats, depression of the heart and respiration, intense saffron-coloured urine, tremor, convulsions and death. Sometimes a rash appears on the skin. Poisoning occurred in a child from 1½ grs. On the other hand, recovery has taken place after swallowing 1 oz. of the drug. These poisonous symptoms have probably been due to impurities.

THERAPEUTICS

Internally.—Santonin is chiefly employed for killing round-worms. It should be given at night on an empty stomach, after a mild purge in the morning, followed by a purgative next morning. Calomel is the best purgative to use. To a child 1 to 3 years old 1 to 2 grs. of santonin may safely be given followed by a purgative next morning. The best method is to prescribe it with calomel and sugar, followed, if necessary, by a dose of Gregory's powder or a saline next morning. It should be taken for three alternate nights. To avoid any toxic effects, castor oil should not be used with it. Crude yellow santonin is regarded by some as a valuable remedy in sprue. But it appears that without special diet it has no influence in modifying the course of the disease and that it is in no way a specific remedy.

CLASS B: Anthelmintics for Tape-worm

FILIX AS

Male Fern. (*Filix Mas.*)

Syn.—*Aspidium*.

Source.—The rhizome and leaf-bases of *Dryopteris Filix-mas*. Collected late in the autumn, divested of roots, leaves, dead portions, and carefully preserved.

Characters—From 7 to 15 cm. or more long. Rhizome about 2 cm. in diameter, entirely covered with curved angular, dark-brown bases of the fronds, which bear numerousramenta; brown externally, green internally. Transverse section shows 8 pale yellow fibrovascular bundles. Odour, slight. Taste, first sweetish and astringent then bitter and nauseous.

Composition.—(1) *Filmarone*, $C_{47}H_{44}O_{16}$; an amorphous substance to which its properties are due, in solution it slowly decomposes into

Filicic acid and *Aspidinol*, (2) *Flavaspidic acid*, and (3) *Albaspidin*. *Filicin* is an anhydride and a modification of *filicic acid*.

B.P. Dose.—60 to 180 grs. or 4 to 12 gm.

OFFICIAL PREPARATION

1. **Extractum Filicis.** *Syn*—*Liquid Extract of Male Fern*, *Oleoresina Aspidin*.—Contains 25 p.c. w/w of *Filicin*. B.P. Dose.—45 to 90 ms. or 3 to 6 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Male fern is a safe and reliable anthelmintic for tapeworm (*Tænia solium*, *T. Mediocanellata* and *Dibothriocephalus*), but being a local irritant it causes vomiting. It should be given in fairly large doses (1 to 2 drs.) to adults on an empty stomach preferably in two divided doses, after the bowels have been cleared by a purgative, and should be followed again by a brisk purgative. It also expels *Ankylostomum duodenale*. As a rule the drug is not absorbed and produces no untoward symptoms. In rare cases and when a large quantity is used it acts as a violent irritant to the alimentary tract, giving rise to vomiting, purging which contains blood, and in more severe cases convulsion, coma, dyspnoea and ultimately death from collapse. The purified *filicic acid* is highly poisonous to mammals, and when given by the mouth acts as a gastro-intestinal irritant. It is very soon absorbed and produces toxic symptoms.

Prescribing hints.—The liquid extract is best given in fresh milk or emulsified with fresh mucilage of acacia and flavoured with chloroform water. The patient should lie down after taking the draught, because it is liable to make him sick. It is best given in the morning on an empty stomach after a purge the previous day. It should be followed 1 to 2 hours later by a brisk purgative, either sulphate of magnesia or compound jalap powder. Castor oil should not be used either with or after it, as the absorption of the toxic principle is favoured by the presence of oil. The purgative must be a powerful one so as to weaken the head of the worm and loosen its hold upon the intestine. The head must be carefully looked for in the stools, and if it is not found, a second dose of the drug should be given two or three days later so as to expel it. But if more time is allowed the worm grows again and gets strong.

LL TI INA TANNAS

Pelletierine Tannate. (Pellet. Tann.)

Source.—A mixture of the tannates of the alkaloids obtained from the bark of the root and stem of *Punica Granatum*.

Characters—A light yellow, amorphous powder. Odourless; taste, astringent. Slightly soluble in water, more in alcohol (90 p.c.).

Incompatibles.—Alkalies, lime water, metallic salts.

B.P. Dose.—2 to 8 grs or 0.12 to 0.5 gm.

PHARMACOLOGY

It is a valuable anthelmintic for tape-worm. In large doses it causes vomiting and purging. Pelletierine sulphate being soon absorbed by the stomach cannot kill the parasite in the intestine, and in large doses it produces certain constitutional symptoms such as dimness of vision, giddiness, muscular weakness and twitchings, etc. These symptoms do not follow the use of the tannate.

THERAPEUTICS

Pelletierine should be administered on an empty stomach or better still after a dose of castor oil, and a brisk purgative, such as compound jalap powder should follow its use. Only fresh salts are reliable as they deteriorate on keeping. The decoction of the fresh root-bark is also a valuable tæniacuge.

The rind of the fruit is a valuable remedy for diarrhœa and dysentery. It is often used with good results alone in diarrhœa, and with the rind of *mangosteen* fruit (*Garcinia mangostana*), and with *kurchi* bark (*Holarrhena antidysenterica*) in the form of decoction in dysentery.

CLASS C: Anthelmintics for Hook-worm

CA ONEI T T AC LO I U

Carbon Tetrachloride. (Carbon. Tetrachlor.). CCl_4

Source.—May be prepared by the action of chlorine on carbon disulphide.

Characters.—A clear, colourless, volatile liquid; odour characteristic; taste, burning. Not inflammable. In contact with flame decomposes, giving off an acrid odour. Almost *insoluble* in water; miscible with dehydrated alcohol and ether. Sp. gr. 1.603 to 1.606.

B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

ACTION AND USES

Carbon tetrachloride has been used as a general anæsthetic, but owing to the presence of carbon disulphide as an impurity and the depressant action on the circulation it is twice as toxic as chloroform. It is used as a fire extinguisher, as a rubber and fatsolvent, as an ingredient in certain types of paint, and for delousing of clothes. Its use has been revived by Maurice Hall as an anthelmintic for hook-worm and has been extensively used for the purpose. It is a direct poison to *necator*, but is less efficient in *ankylostoma* infections, not more than 30 to 40 p.c. of the latter being cured. *Oxyuris* is also expelled in large numbers. It has been used with success in *T. saginata*, and Barlow recently used it in *Fasciolopsis* (liver fluke) in China. It is certainly a very effective and safe remedy for hook-worm, the worms being expelled dead and flaccid.

It passes through the stomach unchanged and probably some absorption takes place in both the small and the large gut. Absorption may be hastened by alcohol and fatty food. The bulk of the drug absorbed is excreted by the lungs.

It is cheap and can be obtained in pure and stable form and is more efficacious than most other remedies. Appearance of toxic symptoms is the only drawback and it is a powerful poison to the liver. In the mass treatment considerable number of deaths occurred in the labour forces in the tea districts. Although some of them are attributed to ingestion of alcohol either shortly before or after taking the drug, a few cases can only be explained as due to special idiosyncrasy to the drug which cannot be detected by previous examination of the patient.

Toxic effects.—Chief toxic effects are headache, nausea, vomiting, melæna, tremors, tetany, narcosis and convulsion. Cases of fatty degeneration of the liver, kidney and other parenchymatous organs have been observed in post mortem examination.

To avoid toxic symptoms the treatment should not be given to alcoholics, and no food or alcohol should be given shortly before or after treatment. The liability to liver trouble may be avoided by previous use of glucose, 1 oz. daily, for two days. Administration of calcium and parathyroid counteracts the toxic effects when calcium deficiency is suspected. Ammonium chloride also produces the same effect.

Contra-indications.—Cirrhosis and other diseases of the liver and patients suffering from calcium deficiency.

Prescribing hints.—The usual dose is 2 to 3 c.c. (30 to 45 ms.) for adults preferably in divided doses in gelatin capsules, or dissolved in water, although some (Chopra) prefer a single dose for fear of absorption. For children the dose is 2 ms. for each year up to 15 years. As a rule no preliminary purge or rest in bed is required and the patient can be given the anthelmintic and the purgative (sulphate of magnesia) in one dose in the morning and no food is taken for three hours. This is of great importance in mass treatment. Sometimes it is given in combination with oil of chenopodium. This has the advantage of giving both the remedies in smaller doses, and since their effects on the human host are different and independent they produce no harmful effect, on the contrary act as synergists. The best method is to give 3 c.c. of carbon tetrachloride and 1 c.c. of oil of chenopodium followed by a saline. When round worms are also present, these should be treated first, and one or two weeks should elapse before carbon tetrachloride is given. It forms an uniform emulsion with milk when shaken vigorously, and is an easy and convenient method of administration. Moreover no burning is felt when administered in this way.

It should not be given with oils. The treatment should not be repeated till after a fortnight.

OLEUM C ENOPO II

Oil of Chenopodium. (Ol. Chenopod.)

Syn.—American Wormseed Oil.

Source.—Oil distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum*. Contains not less than 65 p.c. w/w of ascaridole, $C_{15}H_{21}O_2$.

Characters.—A colourless, or pale yellow, liquid; odour, characteristic and pleasant; taste, bitter and burning.

B.P. Dose.—3 to 15 ms. or 0.2 to 1 mil.

ACTION AND USES

The oil has a sharp burning taste and causes nausea and sometimes vomiting with a feeling of warmth in the stomach. It is rapidly absorbed from the intestine, which is paralysed, depresses the heart and respiration and causes a fall of blood-pressure.

It is one of the most efficient anthelmintics for ankylostomum duodenale and also for round-worm. It has the advantage over other anthelmintics of being certain in action, and is one of the safest remedies. The action is due to the presence of *ascaridole*, but the exact mode of action on the worm is not known.

The preparations obtainable in the market vary a great deal in the irritant properties on the gastro-intestinal tract. Ordinary doses do not kill the worms but they are only paralysed, and a purgative helps their expulsion.

It has been used in the treatment of amœbic infection, and when administered in the same way as for the treatment of hook-worm, relieves clinical symptoms and causes disappearance of amœbæ from the stools. It is reliable for cases resistant to emetine.

Poisoning is rare unless it is given in very large doses. The symptoms are nausea, vomiting, abdominal pain, ringing in the ears, deafness, and in fatal cases coma and convulsion, death taking place from respiratory failure. Different samples vary in their activity and some samples are very unpleasant to take.

If the dose is carefully regulated and the persons treated are not unduly debilitated, it is a perfectly safe drug.

It is excreted mainly through the lungs and the kidneys. Large doses may cause albuminuria.

Contra-indications.—Pregnancy, as it increases uterine contraction; advanced cases of heart disease and chronic nephritis. Should be used with caution and in small doses when the heart, liver or the kidneys are disordered.

Prescribing hints.—It is best given in the morning, in

doses of 0.5 c.c. each for three doses every hour, either on sugar or in capsules, the patient being kept on light evening meal. The treatment is repeated every three or five days, until the parasites disappear from the stool. The dose may be taken to be 1 m. per year up to 11 years. For healthy adults, 20 to 30 ms. It can also be given in syrup of glucose. The preliminary purgative is not regarded as essential, but an after-purgative removes the drug from the gut, lessens the risk of toxic action and helps to clear out of the bowels accumulated faecal matter and the decomposing worms. The usual purgative is either magnesium sulphate or castor oil. Oils do not increase but lessen toxicity.

The dose for *ascaris* is 5 to 10 ms. for children on sugar three times a day for two days followed by castor oil.

TETRACHLORETHYLENE (*Not official*).—It has the same action as carbon tetrachloride but is a little more efficacious and less toxic. Alcohol does not increase its toxicity. It should be given in 15 ms. (1 ml) doses every hour for three doses daily for three days. Three hours after the last dose on the third day a saline purgative (sodium sulphate) should be given.

For *ascaris* give a single dose of 10 ms. in the early morning after fasting followed after half an hour by a dose of brisk saline and no food should be given until the bowels move.

Dose.—15 ms. or 1 ml.

HEXYLRESORCINOL (*Not official*).—It is useful both for hook-worm and *ascaris* but is very expensive and is not suitable for mass treatment. Rigid precautions have to be taken before treatment, as it loses its effect when given after food. 0.5 to 1 grm. in capsules should be given on an empty stomach after a purgative the previous evening and no food should be given for four hours after the remedy. An after-purgative is not essential. (*See Urinary Antiseptics*, page 398).

CLASS D : Anthelmintics for Thread-worms

Oxyuris.—These worms inhabit the caecum and therefore rectal injections (*see* page 331) that are so largely used are not of much value except for removing the worms that have travelled down to the descending colon, sigmoid or rectum. It is probable that these often die out naturally, therefore re-infection of the fingers should be prevented. The female worms wander out of the anus at night and deposit eggs on the surrounding skin causing itching and a desire to scratch. The eggs are thus carried by finger nails to the mouth. Drugs used for hook-worms also help the passage of a large number of thread-worms.

GROUP XIII

DRUGS ACTING ON THE KIDNEYS

The kidneys help to maintain the normal composition of the fluids of the body by separating from the blood the waste products of nitrogenous metabolism and other organic and inorganic constituents which are present in excess and which are not required by the body or cannot be metabolised. They help to preserve the alkaline reserve of the body by eliminating the non-volatile acids formed in the metabolic process, the volatile acids (CO_2) being excreted by the lungs. They also maintain the osmotic pressure at a definite level by excreting the excess of water as occasion demands.

Since all substances eliminated by the kidneys are kept in solution it is necessary that sufficient water should be available from the body. It is not possible to reduce the normal water content of the blood, and in order that diuresis may occur there must be an excess of water however small, in the blood, i.e. hydræmia must be present. The hydræmia however is only temporary, for the excess of water passes from the vessels into the different tissues until the pressure becomes equal.

The fact that urea, uric acid, pigments, salts and water which constitute the bulk of the urine are not manufactured by the kidneys, makes these organs of special interest to the pharmacologist. Inasmuch as digestion, assimilation, metabolism and circulation affect the activity of the kidneys, the condition of the urine furnishes a key as to the manner in which the different organs are performing their respective functions.

A healthy man passes about fifty ounces of urine daily, which is acid in reaction and contains about 2.2 p.c. of urea, whereas the blood is alkaline in reaction and contains only 0.05 to 0.1 p.c. of urea. It is evident therefore that considerable change of the fluid takes place during its passage through the kidneys before it reaches the ureters.

The different parts of the kidneys perform different functions. The *glomerulus* helps the passage from the blood to the tubules of a large quantity of fluid of alkaline reaction containing urea, chloride, sulphate, phosphate, etc. The fluid undergoes further changes in the *convoluted tubules*, where its reaction becomes acid, and urea, uric acid and other nitrogenous substances are added by process of excretion, and the urine becomes more concentrated by the reabsorption of some of the water. Cushny holds that glomeruli act as ultrafilters and filter off a fluid containing all the non-colloidal constituents of the plasma, i.e. all the abnormal constituents and most drugs.

The composition of the blood itself exerts considerable influence in the production of diuresis. The plasma proteins, by their tendency to bind water, exert an oncotic pressure which resists filtration of fluid. When the plasma proteins fall below a certain level increased transudation must result. Moreover the water-binding properties of the colloids are influenced by certain crystalloids, and possibly by some of the hormones. Increased alkalinity within clinical limits tends to favour water retention, while acids tend to diuresis.

Other things being equal, the greater part of the watery portion of the urine is excreted from the glomeruli, and this depends upon the glomerular pressure and the amount of blood flowing through it. If the blood flows through the glomerulus at a low pressure, due to resistance to efferent vessels, or if there is any obstruction to renal veins, the secretion of urine is diminished, although the glomerular pressure may be high in the latter case. It is evident therefore that diuresis occurs only when there is a continuous and rapid flow of blood under certain amount of pressure through the glomerulus. The rate of blood flow through the kidneys depends upon the general arterial pressure, the condition of the kidney vessels, and the pressure in the veins. The capillary system of the glomerulus supplied by the vasa afferentia and that of the tubules supplied by the vasa efferentia are antagonistic to each other. When the vasa afferentia dilate and the vessels of the tubules contract, the pressure and the flow in the glomeruli increase, whilst that to the tubules will be less and *vice versa*.

It must not be supposed that the kidneys simply act as filters, inasmuch as they interpose a barrier in the way of excretion for any substance in the blood which can be of use to the tissues; and if the amount of this substance in circulation does not exceed a certain limit, the kidneys do not excrete it. This rule applies to sugar, salt, hæmoglobin and biliary constituents, and like water are retained in the blood up to a certain limit by a corresponding regulation of their

reabsorption by the tubules. Thus sugar is not excreted unless its concentration is above 0.18 p. c. in the blood, and only when this threshold is exceeded that these substances are excreted in the urine. These substances are termed *threshold substances*. On the other hand no such barrier exists to purely waste products, such as urea, uric acid, etc., and these are termed *no threshold substances*.

The mechanism of diuresis is still unsettled, although it is possible that the secretion of urine is controlled by chemical stimuli. Various foreign substances, even the normal constituents of blood, when present in sufficient concentration, stimulate in some way the kidney cells. It is probable that the increased amount of urine which follows the improvement of kidney circulation may be due to the presence of a greater amount of chemical stimuli and other substances which pass through the organ.

Diuretics are drugs which increase the flow of urine. Increased urine may represent an increased intake of water or may be the result of removal of fluid from the tissues. Diuretics may be classified as follows:—

I *Those acting by increasing the number of glomeruli functioning at a given time.*—Although there are about two million glomeruli in the human kidney, Richards and his associates have shown that all of them do not function at the same time, since the capillaries dilate only in those that are active, the rest remain closed. Each glomerulus together with its tubules forms a renal unit, and diuresis depends upon the number of glomeruli functioning at a given time. Caffeine and urea are supposed to act in this way, thus increasing the filtering surface.

II *Those acting by increasing the flow of blood through the kidney or by raising the glomerular arterial pressure.*—The secretion of urine is largely proportional to the glomerular pressure and the rapidity with which the blood flows through the kidneys. Thus when there is congestion of the renal veins as in failure of compensation, the secretion is diminished, and improvement of circulation by increasing the action of the heart produces diuresis, e.g. by drugs of the digitalis group, caffeine, alcohol, ether, etc. Dilatation of renal vessels as by the use of spirit of nitrous ether also causes diuresis. Similarly by constricting efferent glomerular veins the pressure in the glomerulus may be increased, as by pituitary extract and adrenaline in minute doses.

Accumulation of fluid in the abdominal cavity mechanically hinders the outflow through the renal vessels, and removal of fluid, either by tapping or by purgation, removes venous stasis and produces diuresis.

The glomerular pressure may also be increased by making the blood hydræmic, i.e. by reducing the concentration of plasma protein as (1) by drinking large amount of water, and (2) by injecting normal saline solution, either subcutaneously, intravenously, or into the rectum.

III *Those acting by causing acidosis.*—It has been found that large doses of ammonium chloride and calcium chloride cause reduction of the alkaline reserve of the plasma and act as diuretics. They increase the non-colloidal constituents of the blood plasma and by reducing the concentration of the plasma proteins help diuresis.

IV. *Those acting locally on the kidneys.*—Moderate irritation dilates the renal arterioles and raises the glomerular pressure, while the pressure in the arterial system generally and the resistance in the renal veins, remain unchanged. They stimulate the kidney cells and produce diuresis either by increasing the tubular secretion or by diminishing tubular reabsorption. These are also known as *irritant diuretics*. Except caffeine and its allies most of them irritate the kidney cells causing congestion and even nephritis when given in large doses. They are:—

(a) Glycosides; these are related to the aromatic series, broom (scoparin), cantharidin.

(b) Acids, alkalies and some salts, caffeine, theobromine and other purin derivatives, calomel, mersalyl, novasurol.

(c) *Certain volatile oils.*—Buchu, oils of juniper, copaiba and sandal wood.

V. *Those acting by salt action*—These act by lessening viscosity of the blood, thereby increase the filtrability and raise the glomerular pressure. They also prevent reabsorption from the tubules. The effect is proportional to the osmotic pressure which they exert. Water, urea, acetate and citrate of ammonium, salts, sugar, milk and thyroid extract act in this way.

Therapeutics—The diuretics are indicated to remove either water or solids from the body, and have the following uses:—

(1) Cardiac and pulmonary disorders where the quantity of urine is diminished, or there is chance of dropsy.

(2) To hasten the elimination of waste products or poisonous materials circulating in the blood.

(3) Conditions where there is accumulation of fluid in some natural cavities of the body, as in ascites and pleurisy.

(4) To dilute the urine in inflammation of the bladder and urethra to make it less irritating, and in cases with a tendency to formation of calculi or deposition of solids.

Antidiuretics—Adrenaline in the first stage, when the renal vessels are constricted, diminish the secretion of urine, and pituitary extract in later stage also diminish the secretion of urine and both are *anti-diuretics*. Urine is diminished after saline and hydragogue purgatives and during the toxic stage of digitalis.

Reaction of the urine.—The normal reaction of human urine is slightly acid with a pH range from 5.12 to 7.46, with an average of 6.03. During digestion when the gastric secretion is increased and during fasting the acidity becomes less.

Drugs which increase acidity of the urine.—The urine can be made acid by the use of acid salts, like acid sodium phosphate, or by the use of ammonium or calcium chloride, benzoic acid, boric acid and salicylic acid. The reaction becomes altered or may be highly acid by the use of mineral acids, but in practical therapeutics their usefulness is limited owing to their local irritant effect.

Drugs which make urine alkaline.—We have however more powerful means of making urine alkaline. The salts of sodium, potassium, lithium and calcium which are oxidised in the blood as carbonates and are eliminated as such by the kidneys render the urine alkaline.

Those salts of ammonium that are eliminated as urea have very little effect in making the urine alkaline.

Urinary lithontriptics.—These are remedies employed for dissolving any concretions or calculi formed in the urinary tract or for preventing the deposition of solids from the urine. Alkalies are used in uric acid and oxalate of lime calculi. Benzoates are used when the urine is undergoing alkaline decomposition and phosphatic calculi are liable to be formed.

CLASS A: Diuretics

Water, Caffeine, Theobromine and Sodium Salicylate, Theophylline and Sodium Acetate, Mersalyl, Urea, Oil of Juniper, Scoparium, Apocynum (*see page 281*), Spiritus Ætheris Nitrosi, Digitalis and its allies (*see page 266*), Acetate and Citrate of Potassium and Sodium (*see page 75*), Potassium Nitrate (*see page 79*), Solution of Ammonium Acetate and Citrate (*see page 93*), Punarnava (*q v*)

A UA ESTILLATA

Distilled water. (Aq. Dest.)

Source and characters.—Prepared by the distillation of potable water. A clear, colourless, odourless and tasteless liquid.

A U A S T E I L I S A T A**Sterilised Water. (Aq. Steril.)**

Source.—Distil potable water from a glass still, or a still in which the distillate does not come in contact with copper, which has been cleaned immediately before distillation. Reject the first portion of the distillate and collect the remainder in a sterilised neutral glass container. Close the container to exclude bacteria, and sterilise immediately by heating in autoclave.

PHARMACOLOGY OF WATER

Water forms about 64 p.c. of the body weight and the daily loss from the system is about 100 oz. It is necessary to compensate for the losses caused by the excretory organs and for the repair of the various fluids, and of the solid organs of the body into whose composition it enters. The demand for water is indicated by thirst and an insufficient supply will lead to disturbances of circulation and the heat regulating mechanism and to retention of the products of metabolism.

Water is not absorbed through the unbroken skin, although the epithelial cells slowly absorb it and eventually swell up. Application of cold water causes constriction of the cutaneous vessels and stops perspiration, while hot water dilates the vessels, helps radiation of heat, increases perspiration and lowers temperature. Cold sponging reduces temperature by abstraction of heat. Application of cold water to the body reflexly stimulates coughing and increases inspiratory efforts.

Internally.—Water is very slowly absorbed from the stomach, the normal epithelium of the stomach is scarcely permeable to water. It passes rapidly into the duodenum and is absorbed from the intestine. A large portion is passed out with the stool. When taken mixed with alcohol or carbon dioxide (aerated water) it is absorbed more freely by the stomach.

Taken in moderation with meals it increases salivary, gastric, biliary and pancreatic secretions and helps digestion. As it helps better absorption of foods, less material is left in the gut for putrefactive bacteria. Taken in large doses it causes vomiting, while hot water slowly sipped is a valuable gastric sedative and antiemetic.

Kidneys and skin.—Drinking large quantities of water causes hydræmia and acts as diuretic. It is a common experience to observe increased perspiration and urine when more water is given, and this in proportion to the amount of water consumed. In fact water is the only diuretic and almost all diuretics act by supplying the kidney more water, *i.e.* by making the blood passing through the kidney vessels hydræmic. Drinking of water is accompanied by increased flow of blood and lymph which washes out from the body effete materials and toxins. Injected into the blood pure

water has a tendency to cause hæmolysis by breaking up some of the less resistant blood cells.

Metabolism.—Water flushes the salts and different products of metabolism out of the system. During its passage through the blood and tissues pure water decreases osmotic pressure, and by internal exchange of salt and water between the blood and tissues, and by eliminating the excess material by the kidneys it helps to keep the composition of the blood constant. Nitrogen elimination is increased chiefly in the form of urea, and the sulphates and phosphates are also increased

THERAPEUTICS OF WATER

Externally.—Besides its uses already adverted to in pages 36-38, water, in the form of ice, or constantly changed through a Leiter's coil, is useful in subduing many acute inflammatory diseases, such as meningitis, cerebritis, synovitis, sprains, etc. It contracts not only the superficial blood-vessels, but also those of the organs by reflex action. On the same principle, a local application of ice to the surface arrests internal hæmorrhages, such as epistaxis, hæmatemesis, etc. A sudden partial application of cold to the abdomen, by flapping a wet towel over it, excites contraction of the parturient womb, and is therefore employed in uterine inertia and post-partum hæmorrhage. A smart sprinkling of cold water on the face restores consciousness in hysteria, fainting and narcotic poisoning. The same plan may be adopted in reviving still-born infants. Iced water subcutaneously injected over the diaphragm checks hiccough, and within paralysed muscles improves their nutrition. Ice poultice applied to the chest is used in the treatment of pneumonia. Hot water used as an intra-uterine douche arrests post-partum hæmorrhage.

Internally.—The sucking of ice allays thirst, vomiting and hiccough. A small glass of cold water slowly sipped controls the craving for drinks by stimulating the circulation. In the same manner hot water before meals soothes the irritable condition of the stomach in gastritis, gastrodynia and gastric ulcer. A glass of cold water taken immediately on rising from bed helps the bowels to act. The swallowing of ice arrests hæmatemesis. Copious draughts of water help to wash out minute deposits of **urinary gravel**. If it is a uric acid calculus, drinking of distilled water diminishes the tendency to deposition. As a diuretic Glaessner advocates the oral administration of distilled water for uræmia, hypertension without arteriosclerosis, and urinary lithiasis. Large draughts of water given between meals may arrest the formation of gall-stones by liquefying the bile. As an *emetic*, warm water should not be given in quantities sufficient to

over-distend the stomach, as this may paralyse the muscles and thereby impede rather than promote vomiting. Half to one pint at a time is enough for the purpose. In cedema water is only a safe diuretic when the salt intake is limited. On the other hand its restriction is helpful in acute nephritis and cardiac cedema when the renal circulation fails to deal with normal quantities of fluid. The intake of water should be gradually increased as the kidneys show evidence of being able to deal with it.

CAFFEINA

Caffeine. (Caffein.). $C_8H_{10}N_4O_2 \cdot H_2O$

Syn.—Theine; Guaranine.

Source.—An alkaloid obtained from the dried leaves of *Camellia sinensis* or from certain other plants; or may be prepared synthetically. It is 1:3:7-trimethylxanthine.

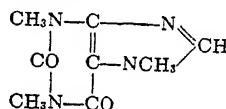
Tea yields 3 to 5 p.c., coffee seeds 1.3 p.c., guarana 5 p.c., *mate* or Paraguayan tea 0.5 p.c., kola nut 3 p.c.

Characters.—Colourless, silky, needles; odourless; taste, bitter. *Solubility*.—1 in 80 of cold water, more in alcohol

(90 p.c.), and in chloroform. The aqueous solution is neutral.

Incompatibles.—Tannic acid, potassium iodide and mercurial salts.

B.P. Dose.—2 to 5 grs or 0.12 to 0.3 grm.



CAFFEINA ET SO II EN AS

(Caffein. et Sod. Benz.)

Caffeine and Sodium Benzoate

Source.—Prepared by mixing caffeine with an equal weight of sodium benzoate. Contains not less than 47 p.c. and not more than 50 p.c. of anhydrous caffeine, and not less than 50 p.c. and not more than 53 p.c. of sodium benzoate.

Characters.—A white powder; odourless; taste, slightly bitter. *Soluble* in 1 part of warm water; completely in 4 parts of water, slightly in alcohol (90 p.c.)

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.; or 2 to 5 grs. or 0.12 to 0.3 grm. (by injection).

NON-OFFICIAL PREPARATIONS

1 *Migraine*. Syn.—*Antipyrin Caffeine citricum*—Soluble in water, contains 9 p.c. caffeine, 1 p.c. citric acid, and 90 p.c. phenazone. In *headache*, but causes sleeplessness. *Dose*—8 to 15 grs or 0.5 to 1 grm

2 *Caffeina et Sodii Salicylas*—Evaporate to dryness Caffeine 5, Sod. Salicylas 5, Water 20. A white amorphous powder containing 47 to 50 p.c. of caffeine. Acts like digitalis, but more rapid. *Dose*—5 to 15 grs or 0.3 to 1 grm. by mouth; 2 to 5 grs or 0.12 to 0.3 grm. hypodermically

3 *Caffeina Citras*—White inodorous powder with an acid reaction. Soluble in 32 parts of water. *Dose*—2 to 10 grs. or 0.12 to 0.6 grm

4 *Iodo-Caffeine* Syn.—*Sodium-Caffeine Iodide*—A white powder, slightly soluble in cold water and freely in warm water. Contains 65 p.c. caffeine. A valuable diuretic in *cardiac dropsy* and *pleurisy*. Useful in *asthma*. *Dose*—2 to 10 grs or 0.12 to 0.6 grm

PHARMACOLOGY

Internally.—Caffeine has three important actions, viz. (1) it is a diuretic; (2) it excites the higher nervous centres;

(3) it acts on all muscle-fibres, whether cardiac, striped or plain.

Heart and circulation.—In medicinal doses it slows the pulse from stimulation of the inhibitory centre and increased vagus excitability. Frequently however no change in the pulse-rate is observed. In some cases the stimulation of the heart is pronounced possibly due to increased flow through the dilated coronary arteries. It increases the absolute strength of the heart and enables it to overcome greater resistance. The systole is increased but it does not increase the diastolic relaxation, which may be reduced, the contraction of the heart-muscle antagonises relaxation and the filling of the heart during diastole (see fig 18). In toxic doses the pulse becomes very frequent, irregular and intermittent, and at last the heart stops in systole. These effects are largely due to the direct action of the drug on the cardiac muscle, chiefly the nodal tissue and the bundle of His, and partly on the cardio-inhibitory centre.

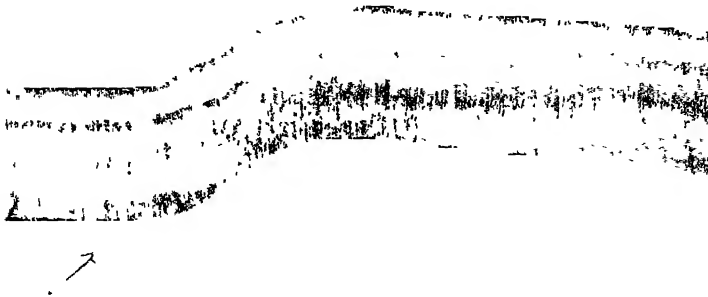


FIG. 18.—Effect of Caffeine on Isolated Rabbit's Heart

At point of arrow a small amount of caffeine was added to the perfused fluid. Note increased tone of the heart. Systole is increased with imperfect relaxation of diastole.

The vaso-constrictor centre is moderately stimulated and this combined with increased output of the heart will tend to cause a rise of blood-pressure; on the other hand there is peripheral vaso-dilatation which overcomes the effect of constriction. In fact caffeine causes a rise of blood-pressure at the beginning but this is offset (generally after 20 minutes) by fall of pressure due to peripheral vaso-dilatation. But this fall in ordinary therapeutic doses is not of much consequence as it is not ordinarily below normal.

An injection of caffeine and sodium benzoate usually causes a slight slowing of the pulse without any appreciable

effect on the arterial pressure. But this often induces undesirable nervous symptoms which precludes it from being used repeatedly without risk of over stimulating the brain and cord. It has no effect on arteries not under control of the vaso-constrictor centre. The coronary arteries are dilated.

Respiration—In therapeutic doses given by the mouth the respiration is moderately stimulated, sometimes however it is scarcely affected unless cardiac dyspnoea is improved by the circulatory effect. The respiration is definitely stimulated when given as an injection.

Temperature is not affected by small doses but is increased by large doses.

Nervous system.—Caffeine in small doses acts entirely on the **higher psychical centres**, this being the only part really affected, hence there is mental exhilaration and removal of fatigue and languor. It has been shown that there is an increase in both the rapidity and accuracy of purely intellectual processes; but caffeine has no effect on those forms of cerebral activity which require a combination of mental processes with physical co-ordination. The perceptions become more acute, pain is more keenly felt, and the sense of touch becomes more discriminating. Caffeine therefore is a **cerebral stimulant**. It increases all conditional reflexes and diminishes all inhibitory processes. In larger doses it stimulates the motor area as evidenced by restlessness, wakefulness, ringing in the ears, delirium and tremors.

Medulla and cord.—The **respiratory centre** is powerfully stimulated, and there is general vaso-constriction due to slight stimulation of the **vaso-constrictor centre**. The **vagal centre** is also stimulated but this is of minor importance since this effect is overshadowed by its action on the cardiac muscle. The motor cells of the cord are also stimulated with acceleration of the passage of impulses like strychnine, but more mildly. It, therefore, increases the reflex activity and improves the tone of the muscle.

Muscle.—Its action is well marked on voluntary muscles. A moderate dose will directly increase the strength and irritability of the muscle; so that a weak stimulus will cause contraction of the muscle; and the total amount of work done before exhaustion sets in is increased. Considering the universal use of beverages containing caffeine it is of practical importance to know that as a result of human experiments with ergograph the increase in muscular power is not followed by a compensatory depression.

Metabolism.—The effect of caffeine on metabolism is not clear. It increases the excretion of xanthine and urea, consumption of oxygen and elimination of CO_2 . There is some rise of temperature due to increased muscular activity and effects on the nervous system.

Kidneys.—Caffeine is a powerful diuretic and it has been

found that under its use the kidney vessels are dilated while causing general vaso-constriction thus increasing the filtration pressure in the renal vessels. But since it acts as a diuretic in the isolated kidney just as well as in the intact animal, the diuresis cannot be due to circulatory changes. On the other hand the evidence is strong that the effect is due to direct stimulation of the renal epithelium, and that the increased flow of blood is the result and not the cause of increased function (Cushny). Verney* asserts that it acts by increasing the number of glomeruli functioning thus increasing the filtration surface. The extent of diuresis varies with the amount of water in the body; and the urine is of low specific gravity, the urinary solids are less augmented than the watery portion of the urine, *i.e.* the diuresis depends upon the amount of filtrable fluid available in the body and becomes less when the accumulated fluid is eliminated and the body becomes relatively "dry". In other words diuresis depends upon an increase of the non-colloidal constituents of the blood which by reducing the osmotic resistance to filtration allows more fluid to pass through the glomeruli into the tubules. It has been found that on a salt-free diet sodium chloride almost disappears from the urine as it is reabsorbed to maintain an adequate concentration of salt in the blood. If however caffeine is administered the salt reappears in the urine. It has therefore been suggested that caffeine *interferes with the reabsorption of salt* by the tubules, as a result of which more salt remains in the tubules which exerts an osmotic pressure and hinders reabsorption of fluids. Moreover there is increased permeability of glomerular cells which allow of increased filtration through them.

As a diuretic caffeine is inferior to theobromine and theophylline, and of these theophylline acts more powerfully on the kidney. Caffeine however does not injure the kidneys when used for a prolonged period even in large doses. It has therefore the advantage over other diuretics and causes no further damage to the kidneys when used in renal disorder.

Absorption and elimination.—Caffeine is rapidly and completely absorbed, only a very small percentage being eliminated in the urine, and none appears in the stools even when given in large doses. About 80 p.c. is completely oxidised into urea, the rest being excreted in the urine as di- and mono-methylxanthine. When used for a long time a certain degree of tolerance is produced so that diuresis is not so marked after some time.

Acute toxic action.—Burning in the throat, thirst, gastro-intestinal pain, violent vomiting and purging, giddiness, tremors in the extremities; free diuresis, clear intellect were observed in a case of poisoning by 60 grs. of the citrate, recovery took place under the use of

**Quarterly Journal of Pharmacology*, 1928.

nitroglycerin. As a rule very few fatal cases occur as a result of caffeine poisoning; possibly the fatal dose is very large, but when taken in doses above 1 grm. it produces alarming symptoms. Even therapeutic doses may give rise to unpleasant side effects.

Treatment generally consists in giving bromides, alcohol and morphine.

Chronic toxic action.—A slow development of the toxic symptoms from excessive tea-drinking is very rare, but is well illustrated in the case admitted into the Bellevue Hospital, New York. Thirty cups per day without food were drunk by him when he got awfully prostrated. Extreme indigestion, extreme anæmia, complete inability to move, great cardiac and respiratory distress were the chief symptoms. In another case symptoms of posterior and lateral sclerosis of the cord were marked.

THERAPEUTICS

Externally.—An infusion of tea is often used as a collyrium in simple conjunctivitis, and a gargle for sore-throat.

Internally. **Heart.**—As a *cardiac stimulant* it is chiefly used as an emergency drug and should not be repeated frequently. It is therefore usefully employed to revive the heart in **cardiac failure** in chronic heart diseases, and may be given either with digitalis or alternating with it. Given hypodermically it is valuable in **acute heart failure in febrile diseases**, e.g. in pneumonia, œdema of the lungs, etc. As it does not possess the permanent tonic action of digitalis, it cannot replace that drug, but may with advantage be used as an adjuvant when a greater effect is desired. It is of signal service in cardiac dropsy specially when combined with digitalis. It may be used to strengthen the heart in many acute diseases, such as pneumonia, fevers, etc. Because it dilates the coronary vessels and relieves vascular spasm, theobromine is used in angina. Effective therapeutic doses however are apt to produce certain side effects, viz palpitation, vertigo, nausea, vomiting, restlessness, sleeplessness, and sometimes delirium, when mental rest and sleep may be of the highest value to the patient. These effects are more apt to occur in patients with interstitial nephritis.

Respiration.—As a **respiratory stimulant** caffeine may be used in œdema of the lungs and depression of respiration. Hot black coffee is largely used in narcotic poisoning to stimulate the respiratory centre. Sometimes it relieves the paroxysms of asthma, possibly by dilating the bronchial muscle, but the effect is weaker than atropine or adrenaline.

Nervous system —In migraine caffeine or the citrate, in combination with aspirin, phenacetin, etc., to assist their action and to prevent their depressing effect on the heart, are sometimes useful. On the other hand Hale has shown that the toxicity of antifebrin and phenacetin is increased by combination with caffeine. Owing to its action on the central nervous system it is used in nervous exhaustion and as

it stimulates the brain and respiratory centre it is used in alcoholic poisoning.

Kidneys.—Caffeine is an uncertain diuretic and has now been superseded by diuretin, agurin and theophylline, but these tend to cause gastric irritation, nausea and vomiting. It is largely used in cases of **cardiac dropsies**, and is of value as a preliminary to digitalis treatment. Its value is not so certain in renal and hepatic dropsies. In chronic parenchymatous nephritis there is as a rule very little response, while in chronic interstitial nephritis it usually gives better results. Many patients get habituated to its use and its diuretic action is entirely lost on them after a week or so. On account of its stimulating action upon the kidney cells caffeine *should not be given* in cases of *acute nephritis*.

Prescribing hints—Caffeine is usually given alone but it may be combined with other drugs, such as strychnine or digitalis as they mutually help each other, or it may be exhibited alternately with digitalis. It should be remembered that the citrate is acid, and when dissolved in water forms an acid solution and dissociates free citric acid. It is therefore incompatible with substances which cannot be prescribed with acids. With iodides it liberates iodine. As an emergency drug caffeine sodium-benzoate should be used hypodermically. When caffeine is used as a circulatory stimulant it stimulates the cerebral cortex, and a few doses may cause excitable nervous condition with wakefulness when sleep may be of the greatest value to the patient. As it stimulates perception it may increase the patient's suffering.

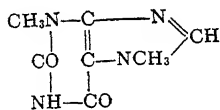
T E O M I N A E T S O D I I S A L I C Y L A S

(Theobrom. et Sod. Salicyl)

Theobromine and Sodium Salicylate

Syn.—Diuretin.

Source.—It is a mixture of sodium theobromine and sodium salicylate in approximately molecular proportions. Prepared by the interaction of sodium hydroxide, theobromine, and sodium salicylate. Contains not less than 46 p.c. of theobromine, 41 p.c. of sodium salicylate, and 6.9 p.c. of sodium.



Theobromine

in ether and in chloroform.

B.P. Dose.—10 to 20 grs. or 0.6 to 1.2 gm.

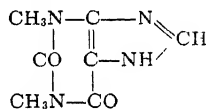
T E P Y L L I N A

Theophylline. (Theophyll.). $\text{C}_7\text{H}_8\text{O}_2\text{N}_4, \text{H}_2\text{O}$

Source.—It is 1:3 dimethylxanthine, an alkaloid obtained from the dried leaves of *Camellia sinensis*, or may be prepared synthetically.

Characters.—A white, amorphous powder. No odour; taste, sweetish and alkaline. *Solubility*.—In equal parts of water. Insoluble in alcohol (90 p.c.),

Characters.—A white, crystalline powder, odourless; taste, bitter. Soluble in 120 parts of water at 25°C., more in hot water; soluble in 80 parts of alcohol (45 p.c.).



Theophylline

OFFICIAL PREPARATION

1 **Injectio Mersalyli.**—Contains about 3 grs. of mersalyl, and about 1½ gr of theophylline in 30 ms. B.P Dose.—8 to 30 ms or 0.5 to 2 mils.

T EOPHYLLINA ET SODII ACETAS

(Theophyll. et Sod. Acet.)

Theophylline and Sodium Acetate

Syn.—Theocin Sodium Acetate.

Source—Prepared by dissolving equimolecular proportions of sodium theophylline and sodium acetate in water, and evaporating to dryness. Contains not less than 55 p.c. of anhydrous theophylline.

Characters.—A white, crystalline powder; odourless; taste, bitter. Soluble in 25 parts of water, insoluble in alcohol (90 p.c.), in ether and in chloroform. Solution alkaline to litmus.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

NON-OFFICIAL PREPARATIONS OF THEOBROMINE AND ALLIED PURIN DERIVATIVES

1 **Theobromina** *Syn*—*Dimethylxanthine*—Isomeric with theophylline. An alkaloid obtained from the seeds of *Theobroma cacao* Dose—5 to 10 grs or 0.3 to 0.6 grm

2 **Theobromina et Sodii Acetas** *Syn*—*Aguin*—A deliquescent powder, easily soluble 1 in 2 of water Dose—10 to 15 grs. or 0.6 to 1 grm

3 **Iodo-theobromine** *Syn*—*Theobromine Sodium-Iodo-Salicylate*—Contains 40 p.c of theobromine in combination with sodium iodide and salicylate In *cirrhosis of the liver, acute nephritis* Dose—2 to 10 grs or 0.12 to 0.6 grm

4 **Theobromine Calcium Salicylate** *Syn*—*Calcium Diuretin, Theocalcine*—Contains 48 p.c theobromine and 11 p.c calcium salicylate A white powder sparingly soluble in water. Action like diuretin Useful in *arterio-sclerosis and asthma* Dose—7 to 15 grs or 0.5 to 1 grm

5. **Theophyllina cum Aethylenediamina**, USP *Syn*—*Aminophylline, Eu-phylline*—White or slightly yellowish granules with a slight ammoniacal odour and bitter taste Contains 70 to 80 p.c anhydrous theophylline. Action same as theophylline but more rapid Valuable in *cardiac asthma, angina pectoris*, and as a diuretic in cardiac and renal dropsy Dose—1½ grs or 0.1 grm by mouth, 7½ grs intramuscularly in 2 c.c. of water, may be given intravenously 3¼ gr in 10 c.c. of sterile water in emergency

6 **Rhodan-Calcium-Diuretin**—In tablets, each contains calcium-diuretin 7½ gr and pot sulphocyanate 1½ gr Dose.—One tablet twice or thrice daily after food.

PHARMACOLOGY AND THERAPEUTICS OF DIURETIN AND OTHER PURIN DERIVATIVES

These substances are called purin derivatives because they are derived from xanthine, one of the purin bases, by the substitution of some of methyl radicals (CH₃) in place of hydrogen.

These derivatives act like caffeine and are powerful diuretics without any side-effects on the nervous system

as possessed by caffeine. Diuresis is due to dilatation of renal vessels, larger number of functioning glomeruli, increased filtration and diminished reabsorption. They however irritate the stomach and produce nausea and vomiting. Attempts have therefore been made to avoid these unpleasant symptoms and also to enhance their action by combining them with calcium, luminal, etc. Theophylline and sodium acetate is more powerful and is more liable to upset the stomach than theobromine and its salt. Theophylline is contained in injectio mersalyli to prevent its decomposition and is used as a powerful diuretic

These closely allied substances differ in their therapeutic action. Caffeine stimulates the heart and has only a slight direct action on the kidneys. Theobromine acts much more powerfully on the renal epithelium, and stimulates the heart and lowers blood-pressure, dilates coronary vessels and relieves vascular spasms. Theobromine sodium salicylate and theophylline ethylenediamine are therefore used in *angina* where they are useful in early cases.

Theocin is a less powerful cardiac stimulant than caffeine but it is a more active diuretic than either of the other two. The best results are obtained with theocin in chronic interstitial nephritis where there is always sufficient healthy kidney tissue left to respond to the drug. It is *contra-indicated in acute nephritis and in diffuse parenchymatous inflammation*. All these diuretics, but specially theocin, increase the solid constituents as well as the water. This places theocin amongst the most efficient of diuretics in cases of oedema with retention of sodium chloride.

Theobromine is usually given either as the double salt with sodium salicylate (*diuretin*), or with sodium acetate (*agurin*). Agurin is free from most of the unpleasant side-effects of diuretin especially the depressing action of the salicylate, while the diuretic action is somewhat increased, since the acetate itself possesses diuretic properties and the amount of theobromine contained in agurin is 10 p.c. more than in diuretin. It is most successful in cases of dropsy due to myocardial degeneration, complicated with nephritis and even in uncomplicated cases.

Theocin is a very powerful diuretic and often acts when both of the above-mentioned combinations have failed; it may either be given alone, or in the form of theophylline-sodium acetate. It is very prompt in its action but the effects soon pass off and it cannot be administered continuously for any length of time. It also produces certain unpleasant side-effects which should be carefully borne in mind. These effects are as follows:—

- (1) Symptoms of gastric disturbance; vomiting and diarrhoea.
- (2) Nervous symptoms; headache, vertigo and convulsions.

These effects are most likely to occur when pure theophylline is used; hence the compound salts should be used in preference, and the following precautions should be observed:—

- (1) The daily dose should not exceed a total of 15 grs.
- (2) The drug must always be freely diluted and given on a full stomach.
- (3) It should only be given on alternate days, using either diuretin or agurin on the intervening day.
- (4) If the patient develops headache or sickness, the drug should be stopped immediately.
- (5) Never use theophylline if there be acute nephritis or excessive destruction of kidney substance. Remember that it only acts when there are healthy kidney cells for it to act upon.

U EA

Urea. $\text{CO}(\text{NH}_2)_2$

Syn.—Carbamide.

Source.—Prepared from ammonium cyanate. It is diamide of carbonic acid.

Characters.—Colourless, transparent, prismatic crystals; no odour; taste, saline, cooling. Soluble in 1 part of water, in 5 parts of alcohol (90 p.c.), insoluble in ether and in chloroform.

B.P. Dose.—15 to 240 grs. or 1 to 16 grm

NON-OFFICIAL PREPARATION

1. Quinina et Urea Hydrochloridum, U.S.P. Syn.—*Urea Quinine*—Contains 58 p.c. quinine. In colourless, translucent prisms. Soluble in water. Used hypodermically in *malaria* and for local *anæsthesia*. Dose, U.S.P.—Hypodermic, 15 grs or 1 grm (one dose only)

PHARMACOLOGY AND THERAPEUTICS

Urea is rapidly absorbed from the intestine and acts as a powerful diuretic by preventing normal reabsorption of water by maintaining the osmotic tension of urine. Since it is rapidly excreted its effects are of very short duration. It is used in the treatment of dropsy. Miller and Feldman* treated cardiac dropsy with massive doses of urea (10 to 25 grm.) thrice daily in 40 p.c. solution with very good results. Some fruit juice is added to cover the taste. When about 50 grm. were given daily most of the œdema disappeared. Some cases regained their cardiac efficiency without the use of digitalis. Because of its property of dissolving uric acid calculi it has been recommended as a preventive and cure for this trouble. As a diuretic it is used in cirrhosis of the liver, gout and chronic kidney diseases.

It is not utilised in the body, and when given in larger doses it is entirely eliminated by the kidneys. Since its

* *British Medical Journal*, Jan. 21, 1933.

elimination is impaired in chronic interstitial nephritis and not in chronic parenchymatous nephritis, it is used as a diuretic in the latter condition. In combination with quinine (urea quinine) it is used in 1 p.c. solution by injection as a local anæsthetic, as a substitute for cocaine. It is non-toxic, soluble in water, and can be sterilised. A 5 to 10 p.c. solution has been injected between the vein and the mucous membrane of the rectum in *internal piles*.

It is supposed to be a true galactagogue.

It is largely used for testing the efficiency of the kidneys, for which purpose 15 grms are given by the mouth and its excretion determined at suitable intervals. Figures below 1.5 p.c. collected one hour after and 2 p.c. after two hours show a poor concentrating power of the kidneys and indicates renal inefficiency. Normal kidneys may concentrate up to 4 p.c. or over.

SPIRITUS AETHERIS NITROSI

Spirit of Nitrous Ether. (Sp. Æther. Nitros.)

Syn.—Sweet Spirit of Nitre. Sp. Æthylis Nitritis, U.S.P.

Source.—Obtained by distilling a mixture of alcohol (90 p.c.), nitric and sulphuric acids, and copper; containing 1.25 to 2.5 p.c. w/v of ethyl nitrite.

Characters.—A transparent faintly yellow, inflammable liquid; odour penetrating apple-like; taste characteristic; sp. gr. 0.838 to 0.842. It should be kept in small sealed amber bottles in the dark. A few crystals of potassium bicarbonate keep it neutral.

Incompatibles.—Potassium and other soluble iodides, iron sulphate, antipyrin, salicylates, tannic and gallic acids, tincture of guaiacum, and emulsions.

B.P. Dose.—15 to 60 ms. or 1 to 4 mls.

PHARMACOLOGY

Externally.—It causes a slight local anæsthesia by evaporation when applied to the skin.

Internally.—It possesses the combined properties of ether and nitrites which it contains, but in a milder degree. It is therefore a mild diffusible stimulant, antispasmodic and carminative.

Circulation.—It accelerates the cardiac activity and relaxes the peripheral blood-vessels, but not to such an extent as the nitrites. By dilating the renal and cutaneous vessels, it acts as a diuretic and diaphoretic respectively and acts as an antipyretic.

Elimination.—It is excreted by the kidneys and the lungs.

THERAPEUTICS

Internally.—Spirit of nitrous ether forms one of the chief ingredients of a fever mixture. It is specially valuable in

fevers during dentition of infants. As a **diuretic**, it is used in **Bright's disease** after the acute inflammatory stage is passed. Dropsies of renal origin are reduced by its use, but it does little good in those of the cardiac type. One of the drawbacks to its use in children is that sometimes it has a nauseating effect.

Vegetable Diuretics

Juniper, Scoparium, Buchu (*see* page 402), Punarnava (*q v*)

OLEUM JUNIPERI (*Not official*)—The oil distilled from the ripe fruit of *Juniperus communis*, and rectified. Colourless or pale greenish-yellow, odour characteristic, taste, aromatic bitter. *Solubility* —1 in 4 of alcohol (95 p c)

Contains (1) *Pinene* ($C_{10}H_{16}$), *Camphene* ($C_{10}H_{16}$), Terpinenol and Cadinene ($C_{15}H_{24}$) (2) Juniper camphor, a crystalline body

Dose — $\frac{1}{2}$ to 3 ms or 0.03 to 0.2 mil

NON-OFFICIAL PREPARATION

1 **Spiritus Juniperi** —1 in 10 *Dose* —5 to 20 ms or 0.3 to 1.2 mils.

PHARMACOLOGY AND THERAPEUTICS

Oil of juniper resembles oil of turpentine in its action, but it is a more powerful renal stimulant and diuretic, and is more agreeable to the stomach. In large doses, it excites the genital organs like cantharidin, causing strangury and priapism. It is absorbed into the blood and is excreted with the urine, to which it imparts an odour of violets. The diuretic effect is observed in dropsy, whilst in health it is said to diminish the urine secreted.

Sometimes it is used as a stomachic, stimulant and antispasmodic, but it is chiefly employed as a diuretic in cardiac and hepatic dropsy, and in chronic nephritis. It should not be used in acute renal affections. It is best given with salines. Gin and Hollands contain it and they can be used as alcoholic beverages in the above diseases.

SCOPARIUM (*Not official*) *Syn.*—*Broom Tops* The fresh and the dried tops of *Gytisus scoparius*. Contains (1) *Scoparin*, a yellow crystalline substance (2) *Sparteine*, a liquid volatile alkaloid, (3) *Genisterine*, a crystalline volatile alkaloid (4) *Savothammne*, a non-volatile alkaloid.

NON-OFFICIAL PREPARATION

1. **Infusum Scoparii Recens**, B.P.C.—Made with *dried* tops 1 in 10 *Dose*—1 to 2 ozs. or 30 to 60 mils

PHARMACOLOGY AND THERAPEUTICS

Broom because of scoparin acts as a valuable diuretic. It is usually prescribed with other diuretics in all forms of dropsy especially cardiac, and interstitial nephritis. *Haustus Scoparii Compositus*, consisting of Potassium Tartrate 20 grs, Sp Juniperi 30 ms. and Infusum Scoparii Rec. ad 1 oz., is a very valuable combination, but it should never be prescribed for acute Bright's disease.

For action of Sparteine, see page 251.

Saline Diuretics

Since all substances eliminated by the kidneys must remain in solution the amount of urine will depend upon the solid contents to be excreted by the urine. The solids that are eliminated by the kidneys are the "low threshold" substances. They are potassium, sodium, ammonium, chlorides, acetates, citrates, nitrates and to a less extent phosphates and tartrates, together with urea and creatinine. These salts are rapidly absorbed and pass into the plasma increasing its os-

motric tension, and since the normal equilibrium has to be maintained, the blood in its turn draws fluid from the tissues making it hydræmic. It follows therefore that any increase in the intake of any of these substances will result in increased diuresis. Being "no threshold" substances they are not reabsorbed from the tubules when they reach the kidney, hence the urinary water is increased and possibly also the glomerular pressure, resulting in an increase of non-colloidal constituent of the blood and increased filtration.

The Saline Diuretics are :—

Chloride of Ammonium and Calcium, and Nitrate of Ammonium (these cause acidosis) Acetate and Citrate of Sodium and Potassium, Acetate and Citrate of Ammonium which are eliminated as urea, Acid Potassium Tartrate and Nitrate of Potassium

CLASS B: Urinary Antiseptics

In order that a drug may act as a genito-urinary antiseptic it must be absorbed through the alimentary canal and excreted by the kidneys. Many antiseptics are however eliminated in an inactive form and are therefore useless as genito-urinary antiseptics. But the drugs of this group are of special value in disinfecting the genito-urinary tract during their elimination in more or less concentrated form. The continual excretion of these drugs through this channel reduces the number of organisms in the urine and prevents sepsis. The action of genito-urinary antiseptics largely depends upon the reaction of the urine which considerably influences the growth of bacteria in the urine. Thus it has been shown that although normal urine undergoes putrefaction in about 36 hours, it takes only 24 hours if rendered alkaline by the administration of potassium salts. On the other hand it takes three days to putrefy if it is rendered acid by the administration of acid sodium phosphate.

The commonly used urinary antiseptics are :—

- 1 Ammonia Formaldehyde Group
Hexamine, Helmitol, Hexyl-resorcinol
- 2 Various acids and their salts
Benzoic acid and Benzoates, Salicylic Acid and Salicylates, Boric Acid, Mandelic Acid
- 3 Certain Essential Oils
Copaiba, Sandal Wood Oil, Buchu, Cubebs (*g v*)
- 4 Coal-tar Dyes
Mercurochrome, Acriflavine, Methylene Blue, Pyridium

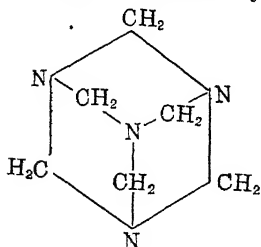
Besides these, certain drugs are used as adjuvants, e.g. the citrates when given in sufficient doses render the urine alkaline, and acid sodium phosphate increases the acidity of urine.

EXAMINA

Hexamine. (Hexamin.). $C_6H_{12}N_4$

Syn—Methenamina; "Urotropine"; Aminoform; Formin.

Source.—Obtained by the combination of ammonia and formaldehyde. Contains not less than 99 p.c. of pure hexamethylenetetramine.



Characters.—Colourless crystals or a white crystalline powder. Inodorous. Taste, at first sweetish, afterwards bitter. Solubility.—1 in $1\frac{1}{2}$ of water and 1 in 8 of alcohol (90 p.c.). Solution alkaline to litmus.

B P Dose—10 to 30 grs. or 0.6 to 2 grms.

NON-OFFICIAL PREPARATIONS

1 **Piperazina**—Formed by the action of ammonia on ethylene dibromide. In small colourless deliquescent crystals, with a strongly alkaline reaction, saline taste and faint odour. Soluble in water. In uric acid diathesis, gout and lithiasis. *Dose*—5 to 15 grs or 0.3 to 1 gm.

2 **Hexamine Glycocholate** *Syn*—*Felamine*—Cholagogue and biliary antiseptic. In *catharrhal jaundice*, after-treatment of typhoid fever and in gallstones. *Dose*—5 grs or 0.3 gm in tablets.

3 **Helmitol**. *Syn*—*Formamol*, *New Urotropine*—A citrate combination of urotropine and formaldehyde. A more powerful antiseptic than urotropine and never causes irritation of the urinary apparatus. *Dose*—8 to 15 grs. or 0.5 to 1 gm.

4 **Pyridium** *Syn*—*Malophen*—Phenyl-azo-alpha-diamino-pyridine hydrochloride. A brick red micro-crystalline powder, slowly soluble in cold water, glycerin, alcohol, etc. A powerful bactericide in gonococcal and staphylococcal infections of the genito-urinary tract. Useful in gonorrhoeal infection and complications of males and females, pyelitis and cystitis. *Dose*—Each tablet contains 1½ gr or 0.1 gm. Two at a time after meals.

PHARMACOLOGY AND THERAPEUTICS

Hexamine is rapidly absorbed and appears in the urine about an hour after administration. The quantity appearing in the urine varies with its absorption, about 20 to 30 p.c. being decomposed in the stomach during digestion, but only about 1 p.c. during fasting when the contents are feebly acid. If used for a prolonged period a concentration of 1 in 2000 can be obtained with a dose of 0.67 gm. It is doubtful whether when administered *per os* it forms enough formaldehyde to retard the growth of bacteria in the urinary tract, for cultures of urine show growth of organisms during hexamine treatment.

It is one of the most powerful urinary antiseptics we possess. But by itself it has no antiseptic power, and its value depends upon the formation of formaldehyde in the acid urine which should be below pH 6. It has been recommended in typhoid fever not only to lessen the chance of cystitis but also to prevent the spread of infection. For the same reason it is largely used in *B. coli* infection of the urinary tract. In this condition the urine is already highly acid and the use of hexamine alone will render the urine sterile. Since acid urine irritates the urinary tract it is often desirable to use large doses of alkalis (citrates or acetates) to make the urine alkaline, and since the growth of colon bacillus is inhibited in an alkaline urine this will not only relieve irritation but will also prevent further growth of the organisms. Meantime hexamine may be exhibited to act as long as the urine remains acid. If the infection of the urinary tract is due to pyogenic cocci or putrefactive organisms the urine becomes foul and alkaline, as in cases of cystitis and pyelitis, and it requires to be rendered acid for hexamine to act. To ensure acidity of the urine acid sodium phosphate should be given in doses of 20 to 30

grs.; or sodium benzoate in doses of 5 to 30 grs.; or ammonium chloride 5 to 20 grs., three times daily. The dose should be adjusted to make the urine acid to litmus. In generalised infection with coli organisms hexamine given intravenously (20 to 40 p.c. solution, 2 to 5 c.c.) gives brilliant results.

It has been used in infection of the gall-bladder, cerebral malaria, pyelitis of pregnancy and post-operative anuria. Although it is said that no formaldehyde is formed in the bile because of its feeble alkaline reaction, to exert any antiseptic effect, Hurst has pointed out that it can produce a disinfectant action when given in large doses (60 to 100 grs. daily). Large doses of alkalies are necessary to keep the urine alkaline to prevent renal irritation. In malarial coma 3 c.c. of a 40 p.c. solution given intravenously will cause the cerebral symptoms to pass off slowly although the parasites remain in the blood. Combined with antitetanic serum it has given remarkable results in tetanus. It has been suggested that hexamine facilitates the entrance of the antitoxin into the cerebro-spinal fluid.

It enters the different organs and secretions freely and has been found in the bile, cerebro-spinal fluid and pancreatic juice. It has therefore been used in cerebro-spinal meningitis, poliomyelitis of children and various inflammatory diseases of the meninges and brain, although there is little evidence that hexamine is converted into formaldehyde in the cerebro-spinal fluid. In fact Otto Mayer suggested the use of 10 c.c. of a 10 p.c. solution with 20 c.c. of air after lumbar puncture in meningitis. He has found good results following its use which he attributes to the hypertonic effect of the drug and not to any disinfectant action.

In combination with sandal wood oil and methylene blue it is often used in gonorrhœa and gleet.

Since formaldehyde forms soluble compounds with uric acid, it has been used in gout, gravel, and uric acid diathesis, but the results have been disappointing. It is specially valuable as a prophylactic after catheterisation.

It begins to be excreted within 10 to 15 minutes and continues for several hours. It should therefore be administered frequently, *i.e.* at least four times a day.

When given in 10 grs. doses it produces so little formaldehyde that the concentration cannot reach the zone at which bactericidal action occurs. On the other hand higher doses are irritating, so hexamine is limited in its usefulness. Nevertheless continued presence of quite low concentration of formaldehyde in the urine has some effect in inhibiting the growth of organisms in cases of chronic infections.

Hexamine itself is not irritant but formaldehyde irritates the bladder and in susceptible persons may cause painful micturition and eventually cystitis and even hæmaturia

HEXYL-RESORCINOL. (Not-official) *Syn.*—*Caprochol.*—1·3 Dihydroxy 4-Hexylbenzol. The introduction of an alkyl radical to resorcin markedly decreases the toxicity and at the same time increases its germicidal activity. A valuable *urinary disinfectant*. It does not irritate the urinary tract, and the germicidal action is not modified by the natural range of the reaction of the urine, but it is destroyed by the use of large doses of bicarbonate of soda. It is more potent in coccal infection than in coli form bacillary infections. It is administered in capsules (0·15 grm. in olive oil) or as 2½ p.c. solution in olive oil. 2 to 4 capsules thrice daily immediately after food or 3 to 6 drs. of the solution, each dr. contains 0·1 grm. Valuable in *cystitis* and *pyelitis*. Produces local necrosis when given hypodermically. *Anthelmintic* for hook-worm (see page 379). Dose—2 to 10 grs. or 0·12 to 0·6 grm.

ACIDUM MANDELICUM (Not official) In white crystals with an acid taste. Soluble in about 8 parts of water; 1 in 2 of alcohol.



CH(OH)-COOH

Dose.—45 grs. or 3 grms. in one ounce of water neutralised with sodium bicarbonate, 4 times daily.

NON-OFFICIAL PREPARATIONS

1 **Sodu Mandelas.**—In white crystals with faintly aromatic smell Soluble 1 in about 1½ of water Dose—50 grs or 3·4 grm.

2 **Ammonu Mandelas**—In white hygroscopic needles, very easily soluble in water and alcohol. Dose—50 grs or 3·4 grm

ACTION AND USES

It has been pointed out that the reaction of the urine has considerable influence not only on the efficiency of urinary antiseptics but also on the bacterial population and naturally many of the methods of treating urinary infections have necessitated some control over the reaction of the urine. While alkalies and alkaline salts judiciously administered will produce satisfactory degree of alkalinity, to render urine acid and to maintain it at a definite pH level is not so easily attained. Apart from drugs, diet also markedly influences the reaction of the urine, and can, if suitably arranged, multiply or reinforce the action of drugs. By giving ketogenic diet the urine can be made sufficiently acid. In fact Clark (1931) by giving patients a diet containing a large quantity of fat and a minimum of carbohydrate caused incomplete combustion of fat with the result that β -hydroxybutyric acid appeared in the urine, which not only rendered urine acid but acted as a powerful bactericidal agent. Since β -hydroxybutyric acid cannot be given by the mouth as it is destroyed in the upper part of the alimentary canal, and treatment of patients by ketogenic diet is unreliable and difficult to control, mandelic acid has been found to be an effective substitute. With an acidity below pH 5·3 it is a powerful bacteriostatic or bactericidal, and is specially valuable in *B. coli* pyuria, cystitis and in pyelitis of pregnancy and puerperium. It is possibly useful in other infections, e.g. *Staphylococcus albus*. Instead of the acid which is more irritating sodium or ammonium mandalate is generally used. The method is to administer sodium mandalate to be preceded by another mixture containing ammonium chloride.*

* No 1 Ammonium Chloride Mixture			No 2 Sodium Mandalate Mixture.		
Ammon chlor	oz	1	Sodium mandalate	oz	1½
Ext glycyrrh liq	ms	240	Syr aurant	oz	1½
Aqua	ad	oz 8	Aqua	ad	oz 8
One table-spoonful in water			One table-spoonful in water,		
4 times a day, before food.			4 times a day after food		

But ammonium chloride often causes nausea and vomiting and therefore ammonium mandalate is preferred, although ammonium chloride requires to be given to obtain the necessary acidity.

To be successful the urine must be strongly acid and the pH value should not rise above 5.3. With a moderate restriction of fluid this degree of acidity is easily obtained, but if it does not then ammonium chloride should be given in 15 gr. doses 4 times a day, or if necessary 5 to 6 times a day, but should not be continued for more than 2 to 3 days in this high dose.

Many proprietary preparations are now on the market which are easy of administration and do not require separate use of other drugs to make the urine acid. These are used in doses of two teaspoonfuls in 2 oz. of water four times a day, after meals. The treatment should be continued for ten days and during this period the fluid intake should be limited to two pints daily in order to ensure a high concentration of mandelic acid in the urine.

Contra-indications.—It occasionally causes diarrhoea, hæmaturia, dysuria, and should not be given when there is impairment of renal function.

C O P A I B A

Copaiba. (Copaib.)

Syn.—Balsam of Copaiba.

Source.—The oleo-resin obtained by incision from the trunks of various species of *Copaifera*.

Characters.—A more or less viscous liquid; generally transparent and occasionally fluorescent, yellow to golden-brown. Odour, peculiar, aromatic. Taste, acrid, somewhat bitter. *Solubility.*—Entirely in an equal volume of dehydrated alcohol.

Composition.—(1) The *Volatile Oil*, 48 to 85 p.c. (2) The *Resin*, 15 to 52 p.c., which remains dissolved in the oil. The resin consists of (a) *Copaivic Acid*, a crystalline resin, and (b) a non-crystallisable viscous resin.

B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.

NON-OFFICIAL PREPARATIONS

1. **Copaiba Resin.**—*Dose*—10 to 20 grs. or 0.6 to 1.2 grms.
2. **Oleum Copaibæ.**—A colourless or pale yellow oil with the odour and taste of copaiba. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally. Gastro-intestinal tract.—It imparts an acrid nauseous taste, and a feeling of warmth to the epigastrium, and gives rise to disagreeable eructations. Continued long it causes dyspepsia and looseness of the bowels.

The volatile oil and the resin are readily absorbed into the blood, and are excreted by the mucous surface of the genito-urinary and respiratory tracts, which they stimulate, producing an increased vascularity and increased secretion which, if foul, is disinfected. Thus copaiba is an expectorant, and a stimulating disinfectant to the genito-urinary surface. It imparts the odour of the drug to the breath, urine and mucous secretions.

Skin.—It is excreted by the sweat-glands, and acts as an irritant to the skin, producing sometimes an erythematous eruption known as "copaiba rash." A portion of it is also

excreted by the milk to which it imparts its nauseous flavour.

Kidneys.—It stimulates the renal cells and is a diuretic. This diuretic action is largely due to the resin. Large doses cause renal congestion, with lumbar pain and scanty, bloody and albuminous urine. The resin and volatile oil are excreted in the urine which they disinfect. As a *powerful diuretic*, both copaiba and its resin have been employed in dropsy, due either to hepatic or cardiac disorder. It is contra-indicated in Bright's disease.

It should be remembered that the resin is inferior to the oil as an antiseptic, but is a powerful diuretic.

On account of its specific action on the gonococcus, it is a very valuable remedy for gonorrhœa. It should be given when the acute symptoms have somewhat subsided in 15 to 20 ms doses, increasing it slowly, as it often upsets the stomach. Its effect is not so marked in gleet

✓ **Prescribing hints.**—Copaiba may be given in capsules, pills, paste, or emulsion. Tincture of quillaia or solution of potash helps emulsification. Cinnamon water, peppermint water, tinctures of ginger and orange fairly cover its unpleasant smell. The oil is best given in capsules or suspended by mucilage. The efficacy of the drug is greatly increased if it is given with sandal-wood oil, cubebs oil, buchu, etc., as in the following prescription*

LEU SANTALI AUST ALIENSIS

(Ol. Santal. Austral.)

Oil of Australian Sandal Wood.

Source.—The oil distilled from the wood of *Eucarya spicata*, and rectified. Contains not less than 90 p.c. w/w of free alcohols, calculated as Santalol, $C_{11}H_{14}O$.

Characters.—A colourless, or pale yellow, oily liquid; with characteristic odour of the wood and unpleasant taste

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

✓ **OLEU SANTALI** *Imperf. - 21547*

Oil of Sandal Wood. (Ol. Santal.)

Syn. I.V.—*Chandaner tel*, Beng.

Source—The oil distilled from the dried heartwood of *Santalum album*. Contains not less than 2 p.c. w/w of esters calculated as →

✓ (*R)

Ol santal	ms. 240
Copaiba	oz 1
Liq pot hydrox.	ms 60
Sp ether nit.	ms 240
Tinct buchu	oz 1
Tinct. hyoscy.	ms. 240
Ol cinnam	ms 10
Mucil acac.	qs.
Syrup	ad oz 6

Mix and make a creamy emulsion. One dessert spoonful mixed with water three times a day after food

santalyl acetate, $C_{17}H_{26}O_2$, and not less than 90 p.c. w/w of free alcohols, calculated as santalol, $C_{15}H_{24}O$.

Characters.—Pale yellow or nearly colourless, viscous liquid; odour, strongly aromatic; taste, unpleasant. Sp. gr. 0.973 to 0.985.

Composition.—The chief constituent is (1) *Santalol*, a mixture of two sesquiterpene alcohols. (2) An aldehyde, *santalal*. (3) Esters, free acids, etc.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATION

1 *Liquor Santali Co*, B.P.C.—Ol. Santal 5, Ol. Cinnam 0.25, Tinct Buchu 17, Tinct Cubebs 15, Alcohol *q s* to 100. *Dose*—1 to 2 dis. or 4 to 8 mls

PHARMACOLOGY AND THERAPEUTICS

Externally.—Sandal-wood oil is used in perfumery. In India it is sometimes applied to scabies with good effects.

Internally—Its action closely resembles copaiba. It is eliminated by the genito-urinary and bronchial mucous membranes, which it stimulates and disinfects, especially the former. It is used with great benefit in 15 to 20 ms doses three times a day in acute and chronic gonorrhœa. When there is much burning, it is a good plan to give small doses (5 to 10 ms) every hour, to prevent the urine from irritating the mucous membrane. Being more pleasant, it can be given as a substitute for copaiba, but the combination of the two gives better results. It must be continued for two weeks, to prevent a recurrence, after the discharge has stopped. It has also been found serviceable in chronic fetid bronchitis and cystitis in 10 ms. doses.

UC U

Buchu

Syn—Buchu Folia, Bucco, Diosma

Source.—The dried leaves of *Barosma betulina*

Characters.—From 12 to 20 mm long, bright green or yellowish-green, rhomboid-obovate, glabrous, somewhat warty, margin denticulate, apex blunt, recurved, with visible oil glands. Odour and taste, strong and characteristic.

Composition—(1) A *volatile oil* (13 to 2 p.c.), containing *diosphenol*, which forms crystalline deposits on exposure (2) *α* limonene, dipentene and menthone, *mucilage* and *diosmin*

BP Dose—15 to 30 grs or 1 to 2 grm.

OFFICIAL PREPARATIONS

- 1 *Infusum Buchu Concentratum*.—40 p c BP Dose—60 to 120 ms. or 4 to 8 mls.
2. *Infusum Buchu Recens*.—5 p c BP. Dose.—1 to 2 oz. or 30 to 60 mls.

NON-OFFICIAL PREPARATION

1. *Tinctura Buchu*, B.P.C.—1 in 5. *Dose*—30 to 60 ms or 2 to 4 mls

PHARMACOLOGY AND THERAPEUTICS

Internally.—The action of buchu is due to the volatile oil which it contains, and it is a **diuretic and mild urinary antiseptic**. In medicinal doses it causes a sensation of warmth in the stomach, and in large doses nausea and vomiting. The volatile oil is readily absorbed into the blood and is mostly

excreted by the kidneys which it stimulates, and partly by the bronchial mucous membrane which is also gently stimulated. During its elimination it soothes and disinfects the urinary passages and imparts a peculiar odour to the urine. It is chiefly used to allay the irritability of the urinary tract, especially the bladder, and is therefore very serviceable in cystitis, irritability of the bladder, urethritis, gonorrhœa, pyelitis, etc. If continued too long in large doses it may harm the kidneys. It is largely used as fresh infusion which forms a good vehicle for mixtures.

CLASS C: Drugs used for diagnostic purposes

- 1 For X-ray Examination **Uroselectan**, **Abrodil**
- 2 Investigation of renal efficiency **Urea** (see page 393), **Indigo Carmine**, **Methylene Blue** (*q v*), **Phenol Red**

UROSELECTAN (Not official). *Syn.*—Iodopyridon Acetate of Sodium. A greyish-white powder, soluble in water. Contains 47 p.c. of iodine in organic combination. Solution neutral.

ACTION AND USES

It is used intravenously to take X-ray pictures of the urinary tract in 30 grm. doses dissolved in 100 c.c. of water. The photographs are taken 15 to 20 minutes after the injection at the time of maximal excretion. As long as the kidneys are healthy and functioning normally the results are satisfactory, but dangerous in acute nephritis. About 95 p.c. of the drug appears in the urine within one and a half hours. It is non-irritating when used subcutaneously.

Uroselectan-B is supplied in sterilised ampoules ready for use. Contains 15 grms. dissolved in 20 c.c. of 10 p.c. solution of invert sugar. It is rapidly eliminated and has the advantage over the earlier preparation in that the quantity injected is less.

ABRODIL (Not official). *Syn.*—Sodium Iodo-methane Sulphonate; *Skrodan*.—A white crystalline powder, soluble in water. Contains 52 p.c. iodine. *Used intravenously* for pyelography for the same purpose as Uroselectan. Solution used is 20 grm. dissolved in 100 c.c. Photographs are taken in 5 to 25 minutes. 4 p.c. solution is isotonic with the blood. About 47 p.c. is excreted in 1 hour and 90 p.c. after 10 hours.

Per-Abrodil is a combination of Diiodo pyridone acetic acid and diethanolamine. Contains 51.8 p.c. diiodine. *Dose*—20 mil of a solution warmed to body temperature intravenously. X-ray photographs are taken after 10 minutes. *Contraindicated* in nephritis, tuberculosis and hepatic disease.

INDICAR INU

(Indicarmin)

Indigo Carmine $C_{16}H_8O_8N_2S_2Na_2$

Syn—Sodium indigotindisulphonate.

Source—Prepared by the action of sulphuric acid on indigotin, neutralising it with sodium carbonate, and precipitating with sodium chloride.

Characters.—A blue powder, or blue granules with a coppery lustre. No odour; taste, saline. *Soluble* in 100 parts of water, readily soluble in warm water. Precipitated by sodium chloride.

B.P. Dose.— $\frac{3}{4}$ to $1\frac{1}{2}$ gr or 0.05 to 0.1 grm. (subcutaneous or intramuscular injection); $\frac{1}{4}$ to $\frac{1}{2}$ gr or 0.008 to 0.016 grm. (intravenous).

ACTION AND USES

It is used either intravenously or by intramuscular injection to test the renal function and for diagnosis of surgical affections of the kidney 4 to 10 c.c. of a 0.4 p.c. solution is usually given intramuscularly into the gluteal muscle. The colour should appear within 7 to 10 minutes, and the depth of the colouration gives a clue to the renal efficiency. It has also been used for the investigation of liver function. After intramuscular injection it is excreted by the healthy subject after 20 minutes and reaches maximum concentration within 2 to 3 hours. When the liver is diseased it is excreted earlier or later according to the nature of the affection of the organ. In diabetes it is earlier, in venous cirrhosis it takes a longer time. In pernicious anæmia it is delayed and the total quantity is less than usual. In cases of jaundice there is no excretion at all in the bile.

PHENOL RED. (*Not official*). *Syn.*—*Phenolsulphonphthalein*.—A white, or faintly yellowish-white, crystalline powder. *Dose.*— $\frac{1}{2}$ gr. or 0.006 grm. by injection.

Uses.—It is used to test the renal function. After an intravenous injection of $\frac{1}{2}$ gr. in 1 c.c. not less than 50 p.c. for the first hour, or 75 p.c. for the first and second hours should be excreted in the urine.

GROUP XIV

DRUGS ACTING ON THE GENITAL ORGANS

Uterus.—The action of drugs on the uterus is difficult to analyse. Experiments made with isolated organs or on intact animals show that the movements are irregular and differ in different animals. The virgin, the pregnant and the non-pregnant uteri also show different types of activity. The movements are myogenic and although not affected by the section of the uterine nerves yet the activity is regulated by the extrinsic nerves. A characteristic feature of the uterine muscle is that it is subject to cyclical changes which occur during menstruation and more specially during pregnancy.

The uterus is supplied by the sympathetic through the hypogastric which contains both the excitator and inhibitor nerves. Stimulation of the sympathetic therefore is followed by a mixed effect, and the contraction or relaxation depends upon the relative preponderance of the two sets of fibres, but this varies in different species of animals and even in the same species, whether virgin or pregnant. The para-sympathetic supply is rather feeble and uncertain and is not generally recognised.

The study of the uterine movements can be made either in the intact animal or in the isolated organ. The movements of the human uterus can be observed with X-rays after filling the cavity with lipiodol; or by using in a bath strips of healthy uterus after an operation and recording its movements.

The pregnant uterus is more sensitive to the effect of drugs than the virgin or non-pregnant one. During pregnancy the uterus undergoes spontaneous contraction which becomes stronger towards the latter part of pregnancy.

The function of the female sex organs is controlled and regulated by a complicated arrangement of the different endocrine glands. The cyclic changes in the ovary are regulated by the anterior pituitary.

The phenomena of menstruation depend upon the state of the endometrium, activity of the ovaries, and the normal secretion of the anterior pituitary gonadotropic hormones. These hormones are responsible for the onset of ovarian activity at puberty, for the regulation of follicular ripening and corpus luteum formation, and their removal is followed by stoppage of menstruation (artificial menopause) with atrophy of the uterus. In congenital absence of the ovaries, or when they are rudimentary, a condition similar to amenorrhœa follows. The luteal hormone, *progesterone*, is of great value for the maintenance of pregnancy, and implantation of ovum cannot occur in the absence of the corpus luteum which enlarges during pregnancy, and its hormone has an inhibitory effect on uterine contraction while its removal in early pregnancy is followed by abortion. Abortion in the early months of pregnancy has been ascribed to excessive production of œstrogen, in relation to that of progesterone. Towards the end of pregnancy the corpus luteum degenerates and the uterus becomes hypersensitive and reacts to an increased secretion of oxytocin from the posterior pituitary resulting in termination of pregnancy.

Ecobolics or *oxytociacs* are drugs which cause expulsion of the contents of the uterus by contracting the uterine muscle. They may be *direct* or *indirect*.

Direct ecobolics act by stimulating the uterus to contraction. They are, histamine, posterior pituitary, quinine, barium and lead which act by stimulating the muscle directly; tyramine, ergotoxine and ergometrine, by stimulating the motor sympathetic endings; and strychnine which stimulates the centre. Hydrastis probably acts in the same way as ergot or pituitary. Of these, pituitary extract, ergot and histamine are most powerful and reliable. Lead is often used as an abortifacient for criminal purposes.

Indirect ecobolics act by producing congestion of the pelvic viscera. They are drastic purgatives and aloes; irritating oils like savine and pennyroyal; irritants like cantharidin, etc.

Emmenagogues are drugs which increase or restore menstrual flow when deficient or absent. They cause congestion of the pelvic viscera. Most ecobolics when used in small doses to non-pregnant women act as emmenagogues. Estrin, the active hormone found in the ovaries and in the urine during pregnancy is chemically related to cholesterol, when injected produces œstrus in rats. It has been found to give relief in cases of artificial menopause and in regulating menstrual disorders. Heat or counter-irritants applied over pelvic regions, e.g. hot hip bath, hot mustard bath or mustard poultice help the onset of menstruation. Amenorrhœa is common in women suffering from anæmia, chronic malaria, cachexia and in general rundown conditions, when appropriate treatment with iron, quinine, codliver oil or other tonics are helpful. Aloe is useful when due to constipation.

Mammary Glands.—These glands are intimately related to the sex glands, and their development is arrested after extirpation of the ovaries, while their growth continues in the normal way after successful transplantation in young animals. Moreover lactosecretory hormone (prolactin, galactin) secreted by the anterior pituitary is essential to initiate and maintain secretion of milk and for the growth of the gland during pregnancy. Just as the development of the glands is regulated by the internal secretion of the ovaries, corpus luteum and the placenta, so also the secretion of milk is regulated by hormones.

Galactagogues are drugs which increase the secretion of milk. An injection of placental extract increases the secretion of milk; so does pituitary extract. The secretion of milk is also influenced by various other factors and reflexes. It is possible that the nerve supply of the mammary glands is different from other glands. Thus pilocarpine, which increases the secretion of other glands, has

no effect on the secretion of milk. Urea is supposed to be a true galactagogue.

Antigalactagogues are drugs which diminish the secretion of milk; as iodides.

Several drugs are excreted by the milk and in doing so alter its composition. Thus rhubarb, senna, jalap, scammony and castor oil may produce looseness in suckling babies, when given to their mothers. Iodides, bromides, arsenic, mercury have been found in the milk when given to women. Copaiba, asafetida, oil of turpentine impart a disagreeable odour to the milk. Opium given to nursing mothers may cause symptoms of poisoning to infants.

Aphrodisiacs—These are drugs which cause sexual excitement and increase sexual power. The centre lies in the lower part of the spinal cord, and excitement can be produced purely reflexly by sensory stimuli from various parts such as the nose, eye, ear, mamma, etc. It is probable that the centre for erection is affected reflexly by the fullness of the bladder and of the seminal vesicles. The centres are also controlled by internal secretions. Steinach has shown that the embracing reflex, which disappears after castration, reappears after injection of testicular substance. This he attributes to the internal secretion of the interstitial tissue and not to that producing spermatozoa. The internal secretions of thyroid and of the hypophysis play important part in the development of the genital organs. Aphrodisiacs are:—Strychnine, damiana, yohimbine, etc.

Anaphrodisiacs are drugs which diminish sexual passion and power. These are iodides, bromides, belladonna, etc.

CLASS A: Echolics

Ergot, Hydrastis, Pituitary Extract

E G TA

Ergot. (Ergot.)

Syn.—*Secale Cornutum*; Ergot of Rye.

Source.—The sclerotium (mycelium or spawn) of *Claviceps purpurea* originating in the ovary of *Secale cereale*, the common rye. Ergot is the diseased rye filled with the mycelium of a small fungus. Contains not less than 0.05 p.c. of the total alkaloids of ergot, calculated as ergotoxine.

Characters.—1.5 to 4 cm. long and 2 to 7 mm. broad, fusiform, obscurely 3 or 4 sided, straight or arcuate; longitudinally furrowed and transversely cracked; brittle; dark violet-black; whitish or pinkish-white internally, showing darker lines radiating from the centre. Odour and taste, characteristic.

Composition.—By the growth of the fungus the proteins of the rye are broken down and various amino-acid derivatives are formed, to which ergot owes its properties. The chief constituents are: (1) The following alkaloids: (a) *Ergotoxine* $C_{28}H_{41}N_5O_6$ an amorphous alkaloid soluble in alcohol, but insoluble in water; sphacelinic acid is an impure specimen of this alkaloid and ergotinine an inert crystalline base. *Ergotamine* resembles ergotoxine if not actually identical. (b) *Sensibamine*, and (c) *Ergoclavine*. Recently another alkaloid, viz. (d) *Ergometrine* has been isolated by Dudley and Moir who gave the formula, $C_{18}H_{23}O_5N_3$, *Ergotocine*, *Ergostetrine* and *Ergobasine* are possibly identical with ergometrine. (2) *Tyramine* or para-hydroxy-phenyl-ethylamine. It resembles adrenaline in action. Derived from amino-acids during putrefaction of organic matter by the elimination of CO_2 . (3) *Ergamine* or *Histamine* obtained from histidine through the agency of putrefactive organisms just as tyramine is obtained from tyrosine. (4) *Agmatine*, an amino-acid derivative, resembles ergamine, but weaker. It also contains fixed oil 30 p.c., tannin, and some colouring matter.

OFFICIAL PREPARATION

1. **Extractum Ergotæ Liquidum.**—Contains 0.06 p.c. w/v of the total alkaloids of ergot, calculated as ergotoxine. After storage contains not less than 0.04 p.c. w/v of ergotoxine, or $\frac{1}{25}$ gr. in 20 ms. B.P. Dose.—10 to 20 ms. or 0.6 to 1.2 mls

E GOTAP AEPA ATA

Prepared Ergot. (Ergot. Præp.)

Source.—It is ergot powdered and immediately deprived of its fat. Contains 0.1 p.c. of the total alkaloids of ergot, calculated as ergotoxine, or $\frac{1}{10}$ gr. of ergotoxine in 15 grs.

B.P. Dose.—5 to 15 grs or 0.3 to 1 grm.

E G TOXINAE AETHANOSULPH NAS

(Ergotox. Æthanosulph.)

Ergotoxine Ethanesulphonate

Source.—Is the ethanesulphonate of an alkaloid, ergotoxine, obtained from ergot. Contains 83.6 p.c. ergotoxine.

Characters.—Colourless, acicular crystals; odourless. Sparingly soluble in water, more in alcohol (90 p.c.), easily in methyl alcohol.

B.P. Dose.— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.0005 to 0.001 grm subcutaneously or intramuscularly.

E GO ETRINA

Ergometrine. (Ergomet.). $C_{19}H_{23}O_2N_3$

Source.—An alkaloid obtained from ergot and purified by crystallisation from a suitable organic solvent.

Characters.—Colourless crystals, which become coloured on exposure to air and light; odourless; taste, slightly bitter. Soluble in water, producing a solution which shows a blue fluorescence; moderately soluble in dehydrated alcohol; sparingly soluble in chloroform.

B.P. Dose.— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.0005 to 0.001 grm.

By intramuscular injection:— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.00025 to 0.0005 grm.

By intravenous injection:— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.000125 to 0.00025 grm.

NON-OFFICIAL PREPARATION

1. **Ergotamine**—In colourless crystals, darkening on exposure to light. Action exactly same as ergotoxine, and is available in the form of **Ergotamine Tartrate**.—Dose.—in *Graves' disease*, 1 mg intramuscularly, $\frac{1}{200}$ gr. subcutaneously, for *migraine*, 2 mg daily by mouth,

PHARMACOLOGY

In spite of the fact that ergot was used to produce uterine contraction and that various alkaloids have been isolated at different times, the chemistry of ergot was only partially solved. It has been observed that although crude preparations of ergot, like the liquid extract, produced uterine contraction within a few minutes, the administration of ergotoxine or any other alkaloid required much longer period to elicit the uterine effect. This was due to the fact that crude ergot contained other active substances which produced the effect, and this was shown by the researches of

Chassar Moir, who elicited definite effects by the administration of watery extract of ergot, and which did not contain any of the known alkaloids. This work was followed by much work and isolation of a new alkaloid ergometrine, and which was soluble in water.

ergotoxine.—($\frac{1}{100}$ to $\frac{1}{50}$ gr.). It has the following effects, viz. (a) stimulates and subsequently depresses the sympathetic myo-neural junctions, but only when they are motor; (b) stimulates the involuntary muscles directly and renders tissues insensitive to adrenaline. It therefore antagonises the motor effects of adrenaline upon the plain muscles. It increases the tone of almost all the plain muscles throughout the body, but the action on the arteries is most marked,

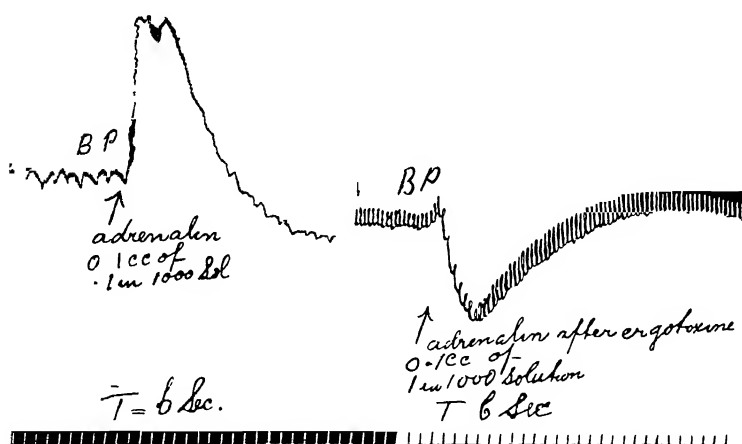


FIG. 19.—Showing phenomenon of Vasomotor Reversal of Dale.

Note the rise of blood pressure with adrenalin and fall of pressure with adrenalin after ergotoxine.

which become constricted with stasis of peripheral circulation. Subsequently there is thickening of the vessel walls and the small vessels contain hyaline plugs. Small doses injected intravenously stimulate the vessels supplied with vaso-constrictor nerves and cause a rise of blood-pressure with slowing of the heart. A second injection causes a smaller rise or no rise at all due to paralysis of the motor nerve-endings of the sympathetic. In small doses it stimulates and in large doses depresses the myo-neural junction of the vaso-constrictor nerves, but leaves the dilators active. An injection of adrenaline at this stage causes the arteries to dilate, the so-called "vaso-motor reversal of Dale." As

it does not influence the inhibitory sympathetic endings, it has no effect on the contracted bronchioles nor on the stomach or intestinal movements. By stimulating the motor sympathetic endings it increases the tone and rhythmic contraction of the uterus. This action is elicited only on pregnant or parturient uterus. It does not constrict the vessels when locally applied, and since its absorption is not retarded from the stomach like adrenaline all these effects are elicited when given by the mouth.

Tyramine ($\frac{1}{2}$ to 1 gr.) acts like adrenaline, but the effects are not so prompt or powerful but are of longer duration. These effects are observed even when it is given by the mouth or injected subcutaneously. It contracts the bronchial muscles and therefore does not relieve asthmatic attacks. It causes marked contraction of the uterus specially when pregnant.

Internally. **Gastro-intestinal tract.**—Ergot has a disagreeable bitter taste and increases salivary secretion.

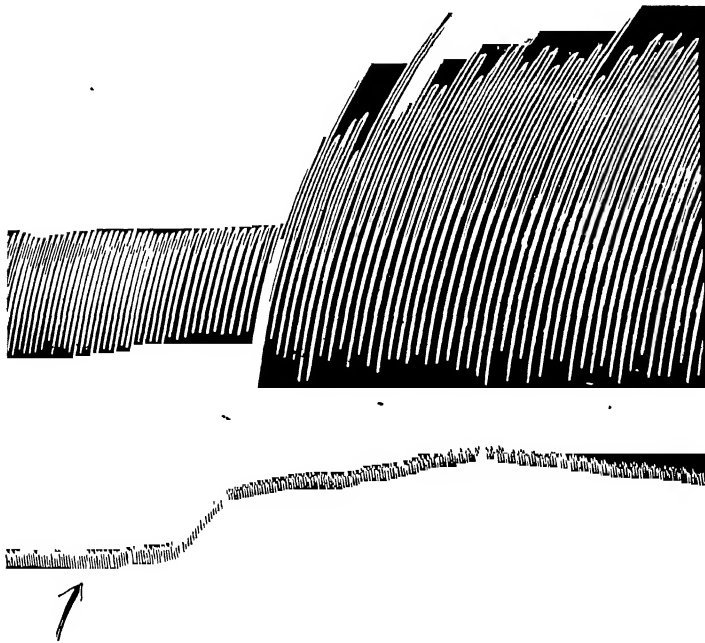


FIG. 20 —Dog. Respiration and Blood-pressure

At point of arrow 0.5 c.c. of 1 per cent solution of ergotoxine was introduced into the femoral vein. Note stimulation of respiration and rise of blood-pressure. After a large dose the respiration is depressed making it slower and weaker.

Since the sympathetic supply to the intestine is inhibitory, ergot has very little effect on the movements of the intestine.

Heart and circulation.—Ergot has decided influence on the heart, which beats more vigorously, the systole is more complete and the output is much greater. This effect is due partly to tyramine exciting the sympathetic nerve-endings like adrenaline and partly to ergamine acting on the cardiac muscle. The rate is slowed from increased blood-pressure stimulating the vagal centre and by the direct action on the muscle.

The effect on blood-pressure is variable, no change being observed unless given intravenously; this is possibly due to the complex action of its different constituents. Given by the mouth there is only a slight rise of pressure partly due to ergotoxine and partly to tyramine causing constriction of the vessels of the abdomen and the extremities by stimulating the nerve terminations in the vessel walls much in the same way as adrenaline. Sometimes when given intravenously there may be a fall of pressure or an initial fall followed by a rise due to the presence in large amounts of histamine or even choline. Prolonged constriction of the vessels caused by ergot, if continued long, may cause gangrene in different parts of the body leading to "gangrenous ergotism." Toxic doses paralyse the vaso-motor centres and the cardiac muscle, producing a fall of blood-pressure.

Uterus.—Ergot powerfully contracts the impregnated uterus of women and lower animals, specially when in labour, thereby expelling its contents. Hence it is a powerful *echolic*. This action is elicited within twenty to thirty minutes after administration by the mouth, and is due to ergometrine and ergotoxine. It is doubtful if ergamine has any share in this effect inasmuch as it will not produce any marked effect when given by the mouth. The contractions become more frequent than the normal ones and also more prolonged. In very large doses the contractions become not only very powerful and remain for a longer time but may become tonic. This may delay delivery and compress and asphyxiate the child, or even may cause rupture of the uterus. In doses given to produce uterine action, ergot has no effect either on the blood-pressure or on the alimentary canal.

Ergometrine is an water-soluble alkaloid introduced by Dudley and Moir. It is non-irritating and unlike the other alkaloids of ergot is rapidly absorbed from the stomach and rectum. Its action differs from that of the alkaloids of the ergotoxine group in that the effects are produced more rapidly, *i.e.* within 5 to 8 minutes when given by the mouth, 3 to 8 minutes when given intramuscularly, and within a minute when given intravenously. It contracts the uterus and the blood vessels by stimulating the sympathetic myoneural junctions, but unlike ergotoxine these are not subsequently depressed. Its effects are less prolonged, lasting

3 to 4 hours, while that of ergotoxine lasts for 6 hours or longer. Moreover when used for a prolonged period it has no gangrene producing properties, and its use is not followed by depression, headache and nausea so common with ergotoxine, ergotamine and ergoclavine.

Respiration.—After an intravenous injection of ergotoxine the respiration is increased both in force and frequency, possibly due to stimulation of the centre. Large doses depress the centre when the respiration becomes slow and weak. Death occurs from asphyxia caused by the spasm of the muscles and weakness of the respiratory centre.

Eye—After a momentary dilatation ergot powerfully contracts the pupil when injected intravenously. This effect is due to the direct action of ergotoxine on the iris, and is not counteracted by atropine.

Nervous system.—It has little effect on the brain. The highest centres are not affected by medicinal doses, not even by a single large dose. It produces changes of a sclerotic nature especially in the postero-external columns of the cord, and induces, when it is given for a long time, a train of symptoms known as "spasmodic ergotism."

Secretion.—The secretion of saliva, sweat, milk and urine is diminished probably from the disturbance of the local blood-supply to the glands by the general vascular contraction.

Acute toxic action.—Acute poisoning is rare but sometimes large doses are taken to procure abortion. The symptoms are weak, rapid pulse, tingling and itching of the skin, excessive thirst, gastrointestinal irritation, uterine hæmorrhage followed by abortion, unconsciousness and collapse. Abortion usually follows, but sometimes even in fatal cases there may be no abortion.

Chronic toxic action or Ergotism.—Poisoning by ergot rarely occurs when used medicinally, but it is very frequently seen amongst the poor who live on diseased rye. It then shows itself under one or other of the two forms described below.

1. **Gangrenous Ergotism.**—Various parts of the body, especially the extremities, suffer from imperfect blood-supply, owing to the contraction and thickening of the walls of the blood-vessels, thereby leading to a process of gangrene. It should not be mistaken for pellagra, a disease characterised by indolent ulcers on the skin, or for Raynaud's Disease.

2. **Spasmodic Ergotism.**—In this variety, the patient first feels a sensation of itching, or tingling, and of insects crawling over the body, followed by a sensation of numbness and of local anæsthesia. These symptoms appear first in the hands and face, then spread over the body. The sensory impairment is soon followed by signs of motor irritation such as tonic contraction of the muscles, especially of the extremities; and later on by the development of a staggering gait. Vomiting and diarrhœa often accompany this variety, and dimness of sight, loss of hearing, and epileptiform convulsions are occasionally present.

It should not be confounded with *lathyrism*, palsy of the lower extremities caused by the use of chick-pea (*Lathyrus sativus* and *Lathyrus cicera*) as the only article of food.

THERAPEUTICS

The chief use of ergot is in obstetric practice to increase uterine contraction. One school advocates its use in all cases with weak contraction as an ecbolic, while others recommend its use only after the expulsion of the child, and will not use during labour, even at the late stage for fear of prolonging labour or even causing death of the child from asphyxia. In any case the use of ergot as an ecbolic should be restricted only to those *cases of uterine inertia in which there is no mechanical obstruction to the passage of the child*; otherwise the child's life may be endangered by the prolonged tonic contraction of the uterus, or if the resistance is too great it may cause rupture of the organ. If however it is used at all the dose should be small and well-regulated so that there cannot be any possibility of the tonic contraction. Ergot therefore is not used as a rule till after the expulsion of the placenta, when it ensures firm contraction of the uterus and prevents **post-partum hæmorrhage**. In multiparas who are often subject to this sort of bleeding, it is a wise plan to administer ergot just after the expulsion of the fœtus, or even before its birth if there be no contra-indication to its administration. In urgent cases ergometrine may be used intravenously; or an injection of pituitary extract may be given along with a dose of ergot by the mouth so that the action of ergot will be manifest by the time the effect of pituitary passes off. It is often given combined with quinine during the puerperium to help involution of the uterus.*

As an internal *hæmostatic* it has entirely lost its reputation; for it is difficult to understand how a drug which causes general constriction of the vessels could stop internal hæmorrhage, as this constriction is attended with general rise of blood-pressure. Its use in any form of internal hæmorrhage other than uterine is irrational. As it increases pulmonary pressure it should not be used in hæmoptysis.

Ergot has been used in many other forms of bleeding from the uterus and sometimes with good results. For instance it is used in menorrhagia, metrorrhagia and in bleeding from various forms of uterine fibroids.

Ergotamine tartrate in the form of *Femergin* (0.001 grm.) has been successfully used in the treatment of migraine and recurrent headaches, either given by the mouth in doses of 1 mg. twice a day or by hypodermic injection in doses of 0.25 to 0.5 mg. ($\frac{1}{20}$ to $\frac{1}{10}$ gr.). It generally arrests the

*R

Ext. ergot. liq	ms. 20
Quinin hydrochlor	gr. 4
Tinct. digit.	ms 5
Sp chloroform	ms 15
Aqua	ad oz 1

attack within an hour. Although oral use is generally ineffective it may be tried in mild cases. The tablets have also been used by sublingual administration and have been found to be more useful. Its action is believed to be due to abolition of the spasm of the cerebral vessels. Urticaria has also been treated with ergotamine tartrate in 2 to 3 mg. doses given orally. It has also been used in Graves' disease.

ISTA INA P SP AS ACI US

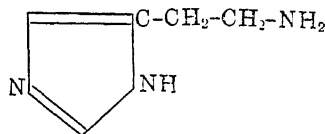
(Histam. Phosph. Acid.)

Histamine Acid Phosphate. $C_5H_9N_3, 2H_3PO_4$

Syn.—Histaminæ Phosphas.

Source.—It is the di-acid phosphate of an organic base, histamine, 4- β -aminoethylglyoxaline. Prepared by the action of phosphoric acid on histamine.

Characters.—Colourless crystals; odourless. Soluble in 4.5 parts of water; slightly soluble in alcohol (90 p c.).



B.P. Dose.— $\frac{1}{15}$ to $\frac{1}{10}$ gr. or 0.0005 to 0.001 gm.

PHARMACOLOGY AND THERAPEUTICS

Histamine occurs in extracts of all vegetable and animal tissues and is formed by the breakdown of proteins in the intestines by the bacterial action. As mentioned elsewhere (see page 286) the absorption of histamine or some amine from the damaged tissue is the cause of shock, either surgical or from extensive burns.

Externally.—A solution of histamine (1 in 1000) applied to the skin and scarified produces what has been termed by Lewis a "triple response." This is characterised by a brief pallor, a definite flare and reddening due to vaso-dilatation and the formation of a local œdema or urticarial wheal. The flare does not appear if the nerves of the skin have degenerated but the œdema appears. This phenomenon has been ascribed to the liberation of histamine-like substance, but this lacks proof.

Internally.—Administered by the mouth it is destroyed by the digestive juices, therefore very little effect is observed when given by this route. Some absorption probably takes place from the intestine and some clinical conditions are due to its absorption from damaged intestine. Injected intravenously or subcutaneously it contracts all plain muscles including the uterus, blood vessels, bronchial and intestinal muscles in the same way as pituitary extract. It contracts both the gravid and non-gravid uterus.

It causes general contraction of the arterioles but the blood-pressure falls and there is failure in the venous return due to generalised capillary paralysis. It also increa-

ses the permeability of the capillaries so that proteins and fluids escape from the vessels into the tissue space which help still further to reduce the volume of circulating fluid. It causes contraction of the coronary arteries of ox, rabbit and man, but dilates, particularly the smaller ones, in cats. Intravenous injection produces symptoms of shock of anaphylactoid type with asthmatic breathing due to contraction of the bronchial muscles. In fact Lewis and Dale attributed all specific sensitiveness to histamine.

In certain species of animals however, e.g. rabbits and guinea pigs, it causes a rise of blood pressure, but in most animals, as mentioned above the pressure falls from dilatation and increased permeability of the capillaries.

It is a powerful **secretagogue**, increases the secretion of saliva, tears, gastric and pancreatic juice, but in man it increases the gastric secretion, specially the acid component in doses that have little or no effect on blood pressure. It has been used hypodermically to test the secretory response of the stomach in gastric disorders to distinguish achylia gastrica from chronic gastritis. If after giving a test meal an injection of 0.5 to 1 mil of 1 in 1000 solution does not provoke secretion of acid, achlorhydria is established.

It has been used hypodermically, by innunction or by ionization in the treatment of chronic rheumatoid arthritis, osteo-arthritis, and related conditions, the initial dose is 0.1 mg. increased by 0.05 mg. in normal saline daily till definite improvement is observed. Satisfactory dose is usually between 0.1 and 0.5 mg. which is repeated 2 or 3 times weekly.

HISTIDINE HYDROCHLORIDE (Not official) *Syn*—L-histidine. A monohydrochloride of the base—histidine, an amino-acid corresponding to histamine.

Dose—3 grs. or 0.2 gm in 4 p.c. solution by subcutaneous or intramuscular injection daily for three weeks.

Histidine is the constituent of most of the simple proteins contained in such food-stuffs like meat, egg, fish, etc. It has been used in the treatment of peptic ulcer on the unsubstantiated theory of Aron and Weiss that such ulcers are due to a deficiency of amino-acid and that administration of histidine corrected that deficiency. At first reports were encouraging and it was used with enthusiasm. Relief from symptoms follows as a rule in 2 to 6 days and some 60 to 90 p.c. cures have been recorded. The advantage of the treatment is that the patient goes through his usual routine work without any restriction to diet. It is however too early to assess its value and already cases are being recorded of disappointing relapses. All that can be said at present is that we have in this drug an added resource for patients who make little improvement on diet-alkali treatment. Moreover daily injections, expense and mild reactions which sometimes occur are also drawbacks for the use of this remedy.

HYDRASTIS RHIZOMA. (Not official) *Syn*—Golden Seal The dried rhizome and roots of *Hydrastis canadensis*. It contains alkaloids (1) *Berberine*, 1.5 to 4 p.c. (2) *Hydrastine* 25 p.c. and (3) *Canadine*.

NON-OFFICIAL PREPARATIONS

1. *Extractum Hydrastis Liquidum*, B.P.C.—2 p c hydrastine *Dose*.—5 to 15 ms or 0.3 to 1 mil.
2. *Tinctura Hydrastis*, B.P.C.—Liquid extract 1, alcohol (60 p c) 10. *Dose*.— $\frac{1}{2}$ to 1 dr or 2 to 4 mils
3. *Hydrastina* *Syn*.—*Hydrastine*—A white crystalline alkaloid. Acts like quinine, though milder. *Dose*.— $\frac{1}{4}$ to 1 gr or 0.016 to 0.06 gm.
4. *Hydrastinæ Hydrochloridum*—A white or creamy white powder. Odourless and soluble in water. *Dose*.— $\frac{1}{4}$ to 1 gr or 0.016 to 0.06 gm.
5. *Hydrastinæ Hydrochloridum*—A pale yellow crystalline powder, soluble in water. *Dose*.— $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 0.016 to 0.03 gm.

PHARMACOLOGY AND THERAPEUTICS

Externally—Hydrastis acts as a stimulant and antiseptic to ulcerated surfaces. It has been employed as a dressing to chronic unhealthy ulcers, and as an application to eczema (5 to 20 grs. in lard 1 oz.). The tincture or the liquid extract (2 or 4 drs to 1 pint) makes an efficient lotion for injection in gonorrhœa after the acute stage, gleet, leucorrhœa, cystitis, etc.

Internally.—Being bitter, it promotes appetite and digestion, and stimulates gastric and intestinal secretion and peristalsis. It is therefore a stomachic and laxative. It contracts the unstriped muscular fibres of the arteries and those of the uterus, hence it is a hæmostatic and ebolic, though the contractions are not so strong as those produced by ergot. The action is direct on the uterine muscle, although there is some stimulation of the hypogastric ganglia which is of minor importance. Hydrastine is a mild febrifuge. On the nervous system its action resembles strychnine, and it increases the reflex excitability and slightly stimulates the vagus, vaso-constrictor and respiratory centres. In large doses it causes convulsions. On the circulation its effects are too uncertain to be of any use therapeutically.

It is one of the most useful remedies we have for chronic gastric and intestinal catarrh, especially of chronic alcoholism. It has been largely employed in arresting hæmorrhages, especially uterine. In short, it may be used in all cases where ergot is indicated. It is however a *weak substitute for ergot* and cannot replace either ergot or pituitary in the treatment of post-partum hæmorrhage. As an antiperiodic it is far inferior to quinine.

TRACTU PITUITARIUM LIQUIDUM

(Ext. Pituit. Liq.)

Pituitary (Posterior Lobe) Extract

Syn.—Liquor Pituitarii; Solution of Pituitary Extract; Pituitrin.

Source.—An aqueous extract of the posterior lobes of pituitary bodies of oxen or other mammals. Contains 10 units per millilitre.

Characters.—A clear, colourless liquid with a faint odour. *Reaction*, between the limits corresponding to the values pH 3 and pH 4.

Composition.—(1) *Oxytocin* or *pitocin*, oxytocic principle, causes contraction of the uterus and without any effect on blood-pressure. (2) *Vaso-pressin*, or *pitressin*, causes rise of blood-pressure and vaso-constriction. Causes both diuresis and anti-diuresis, and relieves postoperative intestinal stasis.

B.P. Dose.—2 to 5 units (0.2 to 0.5 mils) subcutaneously.

PHARMACOLOGY

Heart and blood-vessels.—After an intravenous injection of the extract there is a rise of blood-pressure. A second injection often has no effect if given shortly after the pressure has returned to its normal height. The effect, although

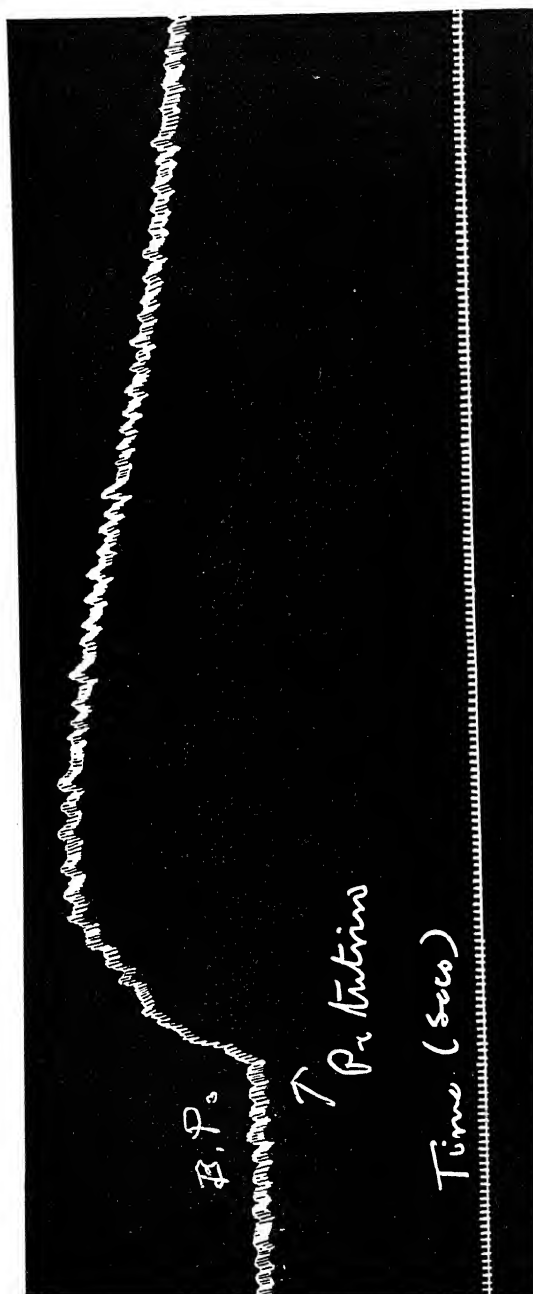


Fig. 21.—Showing the prolonged effect of Pituitrin on Blood-pressure.
Compare the effect of Adrenaline and Ephedrine (page 294)

not so sudden as adrenaline, is more prolonged and lasting. But there is a marked difference in the site of action and the effect is due to the stimulation of the muscles of the arteries and not the myoneural junction of the vaso-constrictors. The arterial pressure begins to rise within a minute and may last for about half an hour. Dale has shown that there is an enormous difference in the strength of different preparations, and in many instances it causes a fall in pressure, a purely histamine-like effect. This is not due to the essential principle but to the presence of some impurity causing depression of the heart. It also constricts the coronary, pulmonary and cerebral arteries. Removal of the gland causes loss of tonus of the capillaries of the frog which is restored by the administration of the extract. It is possible that the pituitary secretes a substance which maintains the normal tone of the capillaries and that substance is vasopressin.

It slows the heart due partly to stimulation of the vagus centre from increased blood-pressure and partly from its direct action on the cardiac muscle. The rate is quickened during the fall of pressure. Whether the rate is slowed or quickened the output of the heart is diminished and the pulmonary pressure falls. In intact animals the heart muscle is weakened from diminished oxygen supply from coronary constriction.

Absorption.—It is not absorbed by the unbroken skin and administered by the mouth it is destroyed by the digestive juices. Given per rectum or applied to the nasal mucosa it is sufficiently absorbed to elicit antidiuretic effect and contraction of the uterus. Full therapeutic effects are elicited when given subcutaneously or intramuscularly. The pressor effect is well marked after intravenous use.

Alimentary canal.—It decreases salivary, gastric, pancreatic and intestinal secretions. Both subcutaneous and intravenous doses have a marked effect on the intestinal muscles causing increased tone and peristalsis. This effect is antagonised by atropine. Quigley and Barnes have however shown that the gastro-intestinal movements are depressed by both the active principles in intact animals. The effect on excised strips of intestine is that of stimulation, though variable and complex.

Kidneys.—Its use is followed by diuresis which is the result of improved renal circulation and high blood-pressure. But this is followed by diminished secretion which is of longer duration. In man and in unanæsthetised animals it diminishes the secretion specially when polyuria is present, as in cases of diabetes insipidus. This effect has been differently explained by different observers. Sollmann attributes it to a specific limitation of the water-excreting capacity of the kidneys, while others hold that this is due to the exist-

ence of a special centre in the brain which regulates the water exchange of the body and which can transfer water from the tissues to the blood, thus exciting diuresis. Pituitary is supposed to regulate the function of this centre. Richards has pointed out that the antidiuretic effect is helped by the contraction of the glomerular capillaries. There can be no doubt that the general contraction of the vessels which is also shared by the glomerular capillaries contributes to the antidiuretic effect as this lessens the filtration surface. It is possible however that it stimulates the epithelium of the renal tubules to absorb more water and thus make the urine more concentrated. It is antagonistic to insulin, as direct stimulation of the gland or injection of the extract is followed by hyperglycæmia and glycosuria (Dale and Burn). This antagonism is not a direct chemical one but is performed through the intermediary of the liver. The vasopressin moiety empties the glycogen reservoirs in the liver, while insulin stores up dextrose as glycogen. It increases the excretion of chlorides.

Female generative organs.—Pituitary by virtue of oxytocin causes powerful contraction of the uterus, whether pregnant or not, by acting on the uterine muscle. In guinea pigs it causes contraction of isolated virgin uterus and this is used for the assay of pituitrin. Some hold that on the human uterus its action is only elicited during labour. But this is doubtful and pregnant human uterus whether in labour or not show marked contraction to pituitrin. The effect is more rapid (occurring within $2\frac{1}{2}$ minutes) and lasts for a shorter time (less than an hour) than ergot. It differs

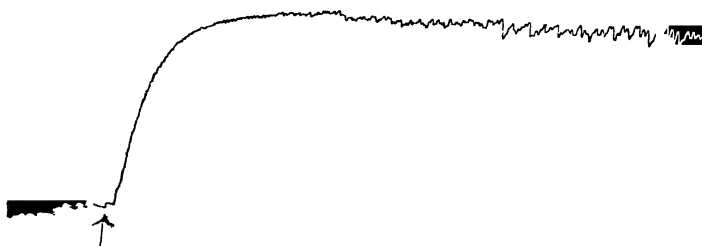


Fig 22.—Effect of pituitrin on the Isolated Uterus (non-gravid) of guinea-pig suspended in oxygenated Ringer's solution. Contraction is indicated by the up-ward movement of the lever

from adrenaline in that it acts on all animals and has no effect on the nervous mechanism. This action is more marked than its effect on the intestine and is elicited whether

the drug is given hypodermically or intravenously. It increases the secretion of milk and is a galactagogue. It does not actually increase the amount of milk secreted, but only helps the expulsion from increased contraction of the unstriated muscles of the milk glands.

Respiration—Respiration is first strengthened and then becomes shallow and slow. After repeated injections no effect is produced. Sometimes bronchial muscles are contracted due to the presence of histamine as an impurity. Pure preparations have no such effect.

The actions of pituitrin and adrenaline are compared in the following table:—

Pituitrin	Adrenaline
1. Causes rise of blood-pressure, action not so rapid and the effects last longer.	Causes rise of blood-pressure action more rapid, and the effects of shorter duration
2. Slows and weakens the heart.	Accelerates the heart.
3. Constricts the coronary and pulmonary vessels.	Dilates coronary vessels.
4. Acts as a diuretic from passive dilatation of the renal vessels followed by oliguria.	Constricts renal arteries.
5. Stimulates the intestine, bladder and pregnant uterus.	Inhibits.
6. Acts directly on the muscle fibre.	Stimulates the sympathetic nerve-endings.

THERAPEUTICS

For its powerful action on the blood-pressure pituitary extract is largely used in the prevention and treatment of shock, specially occurring during the anæsthesia of severe surgical operations

The chief use of the drug is in obstetric practice and it is the most valuable means of strengthening weak labour pains and arresting post-partum hæmorrhage. Its use therefore, has been suggested in the second stage of labour when it helps expulsion of the fetus. Since it stimulates uterine contraction during puerperium it is used preliminary to the use of ergot after the expulsion of the placenta or just before its expulsion to ensure firm contraction and arresting post-partum hæmorrhage. Its use however should be restricted to those cases of uterine inertia where there is no mechanical obstruction to the passage of the child. When used to strengthen labour pains it may, through powerful contraction, actually delay the birth of the child or may cause asphyxia, premature separation of the placenta, or even injury to the soft parts.

Because it causes contraction of the intestinal muscles, it is used in tympanites and intestinal paralysis such as those which may occur after surgical operations, or as a complica-

tion of some acute infection. It is doubtful whether it does good in all cases, and in advanced cases of intestinal paralysis following an infection, it has often been found to fail. Recently its use has been suggested in gastric ulcer and hyperchlorhydria on the idea that it decreases gastric acidity by increasing the excretion of urinary chlorides, thereby diminishing the chloride content of the blood.

As pituitary is an outgrowth of the nasal mucosa, it might be absorbed by spraying into the nose, or from plugs of cotton wool soaked in the solution of the extract and inserted high up into the nasal cavity. This method of treatment has been used with success in diabetes insipidus. In fact the administration of the posterior lobe extract diminishes polyuria, relieves thirst and increases concentration of the urine. To be effective it should be given either as *intranasal spray* or *hypodermically*. Because of its antagonism to insulin, it may be used to counteract hypoglycæmia following an overdose of insulin.

The whole gland pituitary extract is useful in obesity of pituitary origin which is characterised by deposition of fat around the girdles and commonly occurs in children and adolescents. It is usually given in combination with thyroid extract $\frac{1}{2}$ gr. each and then working up to a point at which the patient loses one to two pounds a week. The writer is not convinced of its value and has failed to reduce any weight when given to carefully selected cases for prolonged periods.

Pituitary (Anterior Lobe) Extract.—It is an active extract of the anterior lobe which when injected will accelerate growth in the young animal or cause the fully grown animal to grow further, will produce precocious sexual development in young female rats, and will bring on menstruation in monkeys. It produces all these effects through the following hormones, *viz.* (1) *growth promoting hormone*, removal of the gland or insufficiency of this hormone is followed by infantilism; (2) *gonadotropic hormone*, which in the female initiates the cyclic changes in the ovaries at puberty and regulates these changes during active sexual life. This it does through *prolan A* and *prolan B*. In the male this hormone influences both spermatogenesis and the secretion of male sex hormone; (3) *lactogenic hormone*, which influences the growth of the mammary gland during pregnancy and is also responsible for the secretion of milk (*prolactin*); (4) *thyrotropic hormone*, the loss or insufficiency of this hormone is followed by atrophy of the thyroid with reduction of the basal metabolism, which is prevented by the injection of an extract of the anterior pituitary. Injection of the extract, because of the presence of this hormone, in guinea-pigs produces exophthalmos and hyperthyroidism; (5) *diabetogenic* and *ketogenic hormones*, which influence the metabolism of carbohydrate and fat. (6) *adrenotropic hormone*, removal of the gland leads to atrophy of the adrenal cortex; and (7) *parathyrotropic hormone*, evidence of this hormone is not convincing.

It exhibits two types of cells, *viz.* (1) *chromophobe cells*, without any special affinity for dyes, possibly influence the development of secondary sex characters; (2) *chromophyl cells*, which stain readily and have been subdivided according to the character of the granules into *eosinophyl cells* and *basophyl cells*, the former yields the growth-

promoting hormone and the latter helps in the production of sex hormones.

Zondek and Aschheim have shown that the prolans are present in the urine of pregnant women from a very early stage and are as a rule absent from the urine of non-pregnants and males. They have further shown that implantation of the anterior pituitary into immature female rats induces sex maturity, *i.e.* precocious ovarian activity, and the same results are obtained by injecting the blood or urine of pregnant women.

The injection of *prolan A* or an acid extract of anterior pituitary stimulates the ovarian follicles and helps them to ripen and ovulate with liberation of œstrin which sets up the proliferative changes in the uterine mucosa; while injection of *prolan B* or an alkaline extract of anterior pituitary produces luteinization of the follicular walls with rapid formation of corpora lutea and fixation of the ova, inhibition of ovulation in mature chickens, hypertrophy of the uterus and increased lactation. If the urine of pregnant women, which contains the œstrogenic hormone, is injected several times daily for three days into immature rats or mice, it produces hyperplasia of the genital tract and the mamme. This has been used for diagnosis of pregnancy and is known as Zondek and Aschheim test and can be obtained when pregnancy has only lasted for less than a month and remains positive till twelve days after delivery. This test has been of great value in the diagnosis of extra-uterine pregnancy. In the toxæmia of pregnancy strongly positive results have been obtained by this test in the last third of gestation.

Antutrin is prepared from the urine of pregnant women and contains both prolans A and prolans B. The potency of the solution is judged by the amount necessary to cause the formation of corpora lutea when injected into immature female rats (1 c.c. contains 100 rat units). *Dose*—1 to 2 c.c. hypodermically for 10 to 12 daily injections.

Therapeutic Uses—It is supposed to act as a specific in adiposogenital dystrophy, a disease characterised by retarded sexual development, adiposity, lethargy and deficient vital functions. It is also of value in atrophy of the anterior lobe. Dried gland has been used by the mouth and also an extract hypodermically, but it is doubtful if when given by the mouth it produces any marked improvement.

The sex hormone is sold under the name of *Antutrin*, which in relatively small doses has been used in sexual infantilism with amenorrhœa and delayed puberty, functional sterility and dysmenorrhœa and delayed menstruation due to deficiency of the hormone of the corpus luteum. In larger doses it has been used in menorrhagia and metrorrhagia and in the treatment of climacteric hæmorrhage and threatened abortion. The usual dose is 1 c.c. hypodermically, or 1 gr. of the anterior lobe by the mouth.

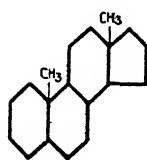
It has been used with success in undescended testis* on the idea that it would stimulate both the development and the descent of the imperfect organ. It is particularly useful in those cases in which the testis has passed through the canal and is occupying the upper reaches of the scrotum. It is possible that it increases the bulk of the testis and the descent is due to gravity. The treatment consists of 3 courses of 6 daily injections or daily injections for 30 days.

SEX GLANDS

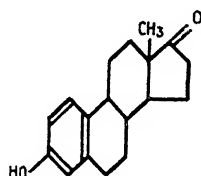
The Ovary—The ovary performs several diverse functions. It is responsible for the development of the secondary sexual characters of women. Menstruation depends upon their proper functioning, while their removal after puberty is followed by atrophy of the uterus, vagina and the external genital structure and cessation of

* Spence and Scowen, *Lancet*, 1935

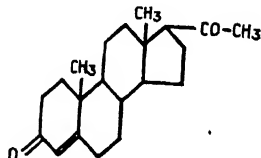
menstruation. In animals the phenomena of 'heat' or *œstrus* do not occur in the absence of ovary. It also helps to fix the embryo into the uterus until it is sufficiently developed to survive birth and to maintain an independent existence. The different hormones isolated from the ovary are (a) *œstrus* producing (œstrogenic) substance or *œstrin* called chemically dihydroœstrone; (b) *corpus luteum hormone* or *progesterone* concerned in the prevention of ovulation and is largely antagonistic to *œstrin*. Both these are sterol compounds and are related chemically to testosterone from the testicle, to vitamin D, and to carcinogenic factor of tar. Apart from progesterone all hormones are bisexual in action. Thus testosterone will restore the structure of the atrophied uterus and vagina of an ovariectomised female, and *œstrin* will cause enlargement of the seminal vesicles and prostate.



Sterol nucleus



Estrone



Progesterone

1. **œstrin.**—It is a term applied to hormones present in the ovaries, placenta, foetal membranes and liquor amnii, and the urine of pregnant women. It can also be obtained from the *testes* and other tissues of the male. It has been isolated in pure crystalline form.

The unit is defined as the specific *œstrus*-producing activity in 0.0001 mg. of the standard preparation which is a hydroxyketonic form of the hormone obtained from urine of pregnancy, and kept at the National Institute of Medical Research, London. The *œstrus*-producing activity is the power of producing in adult female rats or mice, completely deprived of their ovaries, the cellular changes in the vaginal secretion characteristic of normal *œstrus*.

When subcutaneously injected into spayed rats, it produces typical *œstrus*, promotes the growth of uterus and vagina in the immature, causes hyperplasia of the endometrium in the mature, and cornification of the vaginal epithelium; and during labour may sensitise the uterine muscle to the expulsive action of the posterior pituitary. In other words it produces all those changes which facilitate the fertilisation of an ovum.

Since natural or artificial menopause is often accompanied by a variety of nervous symptoms, ovarian extract (which contains *œstrin*), or *œstrin* may be administered in those conditions depending on disordered uterine or ovarian functions, menstrual irregularity and nervous disturbances occurring during menopause, or following artificial removal of ovaries. It has also been used in hyperemesis gravidarum, sexual frigidity and in hypofunctions of the ovaries, e.g. amenorrhœa, functional sterility and genital hypoplasia. It has been used with success in gonorrhœal vulvo-vaginitis of children to produce proliferation of the vaginal mucosa and desquamation of the epithelium.

It may be administered in the form of desiccated ovary in doses of 1 to 10 grs. by the mouth; or as *œstrin* or theelin by hypodermic or intramuscular injection, daily or on alternate days, for six to eight injections. Since it is said to be absorbed from the vaginal mucous membrane it is used in the form of pessaries.

PROPRIETARY PREPARATIONS

1. **œstroform**—*Ketohydroxyœstrin*.—In tablets for oral use containing 1000 units; in ampoules containing 1000 or 10,000 units per ml

2 **Progynon**—Ovarian follicular hormone biologically standardised
Dose.—2 to 3 dragees daily (each of 150 mouse units) and 3 to 6 injections
 of 1 mil (100 mouse units) weekly

3 **Theelin**—It is keto-hydroxy-oestrin. Contains 200 i.u. per mil. Used
 as injection or as pessary. **Theelin in Oil** contains 1000, 2000 and 10,000
 i.u. per mil. *Dose*.—200 to 10,000 units

4 **Theelol** is effective when given by the mouth. It is trihydroxyoestrin.
Dose.—1 to 3 capsules daily, each capsule contains 400 and 200 i.u.

2. **Corpus Luteum**—Its hormone *progestin*, or an extract of corpus luteum administered to virgin animals produces growth of the mammary glands, and it is supposed to control the changes in the uterus which precede the fixation of the ovum, and controls the development of the mammary glands during pregnancy. The gland enlarges during pregnancy and it has been suggested that its hormone (*progestin*) has an inhibitory effect on the uterine contraction. Its persistence depends on the secretion of anterior pituitary hormone, *prolan B*, and when this fails towards the end of pregnancy it degenerates making the uterus hypersensitive which reacts to an increased secretion of oxytocin and finally leads to the termination of pregnancy. On the other hand injection of *prolan B* causes persistence of the corpus luteum and prolongation of pregnancy beyond the normal term.

Corpus luteum, *progesterone* or *progestin* is useful in sterility and habitual abortion due to deficiency of the corpus luteum, but is contra-indicated in sterility of ovarian origin. Since it is probable that it suppresses menstruation it may be of value in menorrhagia. Usual practice is to give daily injection of 1 unit for two months beginning a month before the usual time for abortion. In threatened abortion, determine if possible whether the foetus is alive, and one unit should then be given daily until bleeding and the pain disappears. In functional menorrhagia 1 unit should be given daily in the premenstrual period and during the actual time of bleeding, while 500 units of the anterior pituitary factor should be injected daily then, and three times a week during two months apart from these events.*

PROPRIETARY PREPARATIONS

1 **Gestone**—Pregestational hormone of corpus luteum. *Dose*.—1 to 2 units intramuscularly daily.

2 **Lipo-Lutin**—Solution of *progestin* containing 1 rabbit unit per mil. *Dose*.—1 to 2 mil.

3 **Proluton**—Solution of corpus luteum hormone. In menorrhagia, metrorrhagia and habitual abortion.

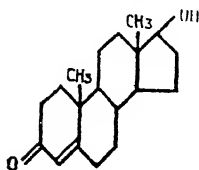
4 **Stilboestrol**—4,4 dihydroxy- α - β -diethylstilbene—A synthetic oestrogenic substance. Less expensive than the natural oestrogenic hormone and active when given by the mouth, *Dose*.—In tablets of 0.5 mg., 1 mg., and 5 mg., in ampoules of 1 and 5 mg. in oily solution.

The Mammary Glands.—Mammary substance is related to the uterus and is useful in cases of profuse menstruation of young girls and young women, and the menorrhagia occurring at the time of menopause. It is usually combined with pituitary. *Dose*.—2 to 5 grs. of the desiccated gland three times a day.

The Prostates.—The frequency of neurasthenic manifestation in persons suffering from prostatic disorders has led to the belief that prostate supplied some element which normally controls the nervous system. With this idea it has been used in the treatment of neuroses that occasionally follow prostatic hypertrophy. There is no reliable evidence that the prostate furnishes an internal secretion. In fact no demonstrable defect has been noticed after removal of the glands.

*G. W. Corner *Jour. Amer. Med. Assoc.* 1935.

The testicles produce an internal secretion which controls the secondary sexual characteristics. This hormone is known as *testosterone*, and is soluble in oil and obtained from the lipid fraction of bull's testes. In the male urine *androsterone* and *dehydro-androsterone*, which are degradation products of testosterone are found. All these hormones are crystalline sterols and have been prepared synthetically from cholesterol and other sterols. As has been mentioned elsewhere they are chemically allied to female sex hormones, to vitamin D, etc.



Testosterone

Although the development of the secondary sex characters depends upon the internal secretions of the testis, the gonads are influenced by the anterior pituitary (see page 420) which directly controls both spermatogenesis and the internal secretory activity of the interstitial cells.

Transplantation of the testes (Voronoff's operation) is supposed to cause rejuvenation, and has been tried in the Continent and other places. Steinach produced similar effects by ligating vas deferens which caused atrophy of the spermatogenetic tissue and hypertrophy of the interstitial tissue.

Therapeutic administration of male sex hormones has not resulted in any very startling effect, although they have been used in the form of testosterone in sexual infantilism of moderate degree, in atrophy of the testes which may follow an attack of mumps, after castration, in hypertrophy of the prostates, in cryptorchidism, and in sexual impotence with varying results.

The International Unit of testosterone is the activity of 100 microgrammes (0.1 mg.) of androsterone as assayed by the growth response of the comb in capons. Dose.—1 ml (=2 comb growth units) by intramuscular injection twice or thrice weekly for 10 injections

CLASS B: Uterine Sedatives

These are remedies which inhibit uterine contraction, and are therefore of value in the treatment of threatened abortion. They should be avoided during labour as they are liable to cause uterine inertia. Few drugs, however, actually inhibit the uterine contractions, although narcotics and general anæsthetics cause some delay in labour through their effects on the central nervous system. Atropine diminishes uterine contraction by depressing the motor nerve-endings. Apart from these, certain drugs possess the reputation of being uterine sedatives, and are used in *threatened abortion*, *dysmenorrhœa*, etc. Drugs which relax plain muscles generally also reduce uterine contraction, e.g. nitrites and papaverine. Corpus luteum has the property of reducing the sensitiveness of the uterus to œstrin and also diminishes spontaneous movements during pregnancy. It is therefore sometimes used in cases of threatened abortion.

VIBURNUM (*Not official*). *Syn*—*Black Haw*—The dried bark of *Viburnum prunifolium*. Contains (1) *Viburnin*, a glycoside (2) A resin (3) Valerianic, tannic, and gallic acids

NON-OFFICIAL PREPARATIONS

- 1 **Extractum Viburni Liquidum**—1 in 1 Dose —1 to 2 drs or 4 to 8 mls
- 2 **Elixir Viburni et Hydrastis**, B.P.C.—Ext Viburnum, Liq Ext Hydrastis, Ol Coriander, Ol Caraway and Glycerin. Dose —1/2 to 1 dl or 2 to 4 mls
- 3 **Extractum Viburni**, B.P.C.—Liquid extract by evaporation Dose —3 to 8 grs or 0.2 to 0.5 gm.

PHARMACOLOGY AND THERAPEUTICS

It has been used as a sedative in neurotic and hysterical affections but its chief use is as an uterine sedative. It is supposed to diminish

or check uterine contractions occurring during pregnancy and endangering its continuance, and it is therefore used in cases of **habitual abortion**, when this does not arise from any specific cause such as syphilis or nephritis. It is used extensively in all sorts of uterine troubles, but in therapeutic doses it is of no value at all.

GROUP XV

DRUGS HAVING ANTI-PYRETIC, ANTI-PERIODIC
AND ANTI-SEPTIC PROPERTIES

- Class A Anti-pyretics and Analgesics
 Amidopyrine, Phenacetin, Phenazone, Acetanilide
- Class B Anti-periodics
 Cinchona Bark, Quinine, Quinidine, Plasmochin, Atebrin
- Class C Anti-pyretics, Antiseptics and Anti-rheumatics
 Salicylic Acid, Salicylates, Methyl Salicylas, Benzoin, Benzoic Acid, Benzoates

ANTI-PYRETICS AND ANALGESICS

Antipyretics or Febrifuges are remedies which lower the temperature of the body in pyrexia.

Antipyretics, except when given in toxic doses, have very little effect upon the temperature in health but they act powerfully when it has been raised above normal. The maintenance of the body heat at about 98.4°F. is the result of a fine adjustment between heat production on the one hand and heat dissipation on the other, and anything which disturbs this equilibrium will cause either a rise or a fall of temperature as the case may be. Heat is lost primarily from the skin and from the respiratory passages. From the skin by conduction and radiation, and by evaporation of sweat; and from the respiratory passages through warming of the inspired air, and by evaporation of water. A small amount is also lost in the excretion of urine and faeces. Excessive loss of heat is counteracted by (1) contraction of cutaneous vessels which by reducing perspiration diminishes the loss of heat; and (2) increased combustion of tissues, whereby more heat is formed. In order to preserve the equilibrium between these factors there exists a *heat regulating centre* situated in the basal ganglia of the cerebrum and in the neighbourhood of tuber cinereum. Any lesion in its neighbourhood is followed by a rise of temperature, e.g. injury to corpus striatum. With the fall of temperature there is perspiration and flushing of the skin. The amount of oxygen absorbed and CO₂ given out are also diminished.

Antipyretics act in the following ways:—

1. *By increasing loss of heat by acting on the thermogenic centre in the corpus striatum.*—As phenacetin, amidopyrine, acetanilide, phenazone, etc.

2. *By dilating the cutaneous blood-vessels and thus augmenting radiation.*—As alcohol, nitrites, spiritus ætheris nitrosi, salicylates (also act by diaphoresis), warm baths.

3. *By increasing the amount of perspiration and thus causing a loss of heat by evaporation (see Diaphoretics).*

4. *By abstracting heat.*—Cold or tepid water bath, cold wet-pack, cold sponging, local irrigation with cold water, cold water compress, and evaporating lotions are agents by which we can abstract heat and thus increase heat loss.

5. *By neutralising or destroying any specific poison causing pyrexia.*—As quinine in malarial fever, and antidiphtheritic serum in diphtheria.

Caloricrescents are remedies which elevate the body temperature.

The temperature may be raised either by increased heat production or diminished heat loss. Pyrexia occurs only when the change exceeds the capacity of compensation.

The following factors cause a rise of temperature :—

(a) *Heat puncture*, i.e. injury to the neighbourhood of corpus striatum. The rise of temperature is due to increased production and does not occur in glycogen-free animals

(b) *Bacterial toxins* when injected, or produced in the body by infection with living bacteria. Here the rise of temperature is due to diminished heat loss. Heat production is generally increased though not always so.

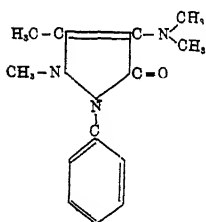
(c) *Certain drugs*. Tetrahydro β -naphthylamine causes rise of temperature of several degrees. There is increased heat production and diminished heat loss from cutaneous vaso-constriction. It is not a central effect as pyrexia occurs after the centre has been destroyed or made inactive by the previous use of antipyretics. Belladonna, caffeine, cocaine, and picrotoxin in toxic doses cause a rise of temperature.

A I PY INA

Amidopyrine. (Amidopyrin). $C_{13}H_{17}ON_3$

Syn.—Pyramidon.

Source.—May be prepared by methylation of the reduction product of the nitroso-derivative of phenazone.



Characters.—Small, colourless crystals, or a white crystalline powder. No taste or odour. Soluble in 18 parts of water, and in 2 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

P NAC TINU

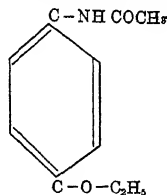
Phenacetin. (Phenacet.)

Syn.—Acetphenetidin

Source.—Obtained by the acetylation of *p*-phenetidine.

Characters.—White glistening, crystalline scales, or a fine, white, crystalline powder. No odour; taste, slightly bitter. Soluble in 1700 parts of water, in alcohol (95 p.c.); solution neutral.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.



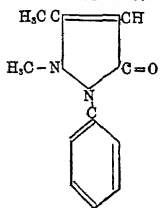
P ENA NU

Phenazone. (Phenazon). $C_{11}H_{12}N_2O$

Syn.—Antipyrin

Source.—It is 1-phenyl-2:3-dimethyl-5-pyrazolone. Obtained by the interaction of phenylhydrazine and ethyl acetoacetate, and subsequent methylation.

Characters.—Small, colourless crystals, or a white, crystalline powder; odourless; taste, slightly bitter. Solubility.—1 in 12 parts of water, in 1.3 of alcohol (90 p.c.), or of chloroform.



Incompatibles.—Spiritus ætheris nitrosi, tannic acid and cinchona preparations. Powdered phenazone liquefies when rubbed with butyl chloral hydrate, sodium salicylate, naphthol.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm

NON-OFFICIAL PREPARATIONS

1. *Phenazoni Salicylas, B P C* *Syn*—*Salipyrin, Antipyrin Salicylate*—White, sweetish crystals, sparingly soluble in water. Analgesic, *antirheumatic*. *Dose*.—5 to 20 grs. or 0.3 to 1.2 grm.

2. *Acetopyrin* *Syn*—*Antipyrin Acetylsalicylas*—A white crystalline powder being a combination of phenazone and acetic acid. Analgesic, *antipyretic, antiarthritic*, without injurious action on the heart. *Dose*—8 to 15 grs. or 0.5 to 1 grm.

3. *Acetanilidum* *Syn*—*Phenyl-acetamide, Antifebrin*—Colourless, inodorous, glistening lamellar crystals, taste, pungent. *Solubility*—1 in 210 of cold, 1 in 18 of boiling water, 1 in 42 of alcohol (90 p.c.), freely in chloroform and ether. *Dose*—2 to 5 grs. or 0.12 to 0.3 grm.

4. *Exalgine. Syn*—*Methylacetanilide*—Colourless acicular crystals. Antipyretic and analgesic. Chiefly used in *migraine, sciatica and neuralgia*. *Dose*.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

PHARMACOLOGY

Locally.—Phenazone and acetanilide are hæmostatics and most of them are also antiseptics, but this effect varies with their solubility and stability.

Internally.—Blood is not affected by the ordinary doses, but its colour is changed by large doses, owing to the formation of methæmoglobin. Antipyrin seems to be devoid of this action. The red blood corpuscles are broken up, become distorted, shrunken and devoid of colouring matter, while part of methæmoglobin might escape through the kidneys, and hæmoglobin and even blood may appear in the urine. This effect is perhaps due to the decomposition of the drugs and the flooding of the tissues with paramidophenol, or the corresponding quinoline derivative.

Heart.—In experimental work the heart muscle is first accelerated by ordinary doses, but in large doses the muscle is weakened and the beat becomes slow and irregular, causing collapse. This action is probably due to the sedative influence on the cardiac muscle. Acetanilide is the most depressant, next comes phenazonum, phenacetin and amidopyrine have little or no depressant action. Collapse occurring from moderate doses is often due to idiosyncrasy.

Blood-vessels.—Acetanilide and phenazone contract the blood-vessels by acting directly on their muscular fibres. These are therefore hæmostatics, phenazone being more energetic than the other. The blood-pressure is raised at first, and is lowered subsequently from cardiac weakness.

Respiration.—The respiratory force is diminished only by toxic doses.

Kidneys.—They slightly increase the flow of urine, urea and uric acid. Large doses cause hæmoglobinuria. Phenazone is quickly excreted and appears in the urine either unchanged or as oxyantipyrine in combination with glycuronic and sulphuric acids. Phenacetin appears as phenetidin compounds. Acetanilide is said to be excreted as aniline.

Skin.—Papular, erythematous, urticarial rashes are ob-

served at times. They may produce a slight diaphoresis in health, but a copious one in pyrexia. Therefore they are **diaphoretics**

Temperature.—All these drugs are powerful **antipyretics**, but the exact mode of their action has been the subject of much controversy. They have very little effect in reducing the temperature in health except when given in toxic doses so as to produce collapse, but they reduce temperature when it is high, as in fever, due to the fact that in fever the heat regulating centre is in an abnormal state and is more susceptible to these drugs. As a rule the temperature begins to fall within two hours and generally comes down to normal or even to subnormal and is accompanied by profuse sweating preceded by vaso-dilatation which is confined to the skin and is a central effect. This was at one time believed to be the cause of the fall, but the temperature falls even when the perspiration is checked by the previous use of atropine or agaricine. The antipyretic effect is the result of direct action on the heat regulating mechanism causing an increased heat dissipation by dilating the cutaneous vessels. In fact the perspiration is preceded by a feeling of external heat and flushing of the face. Amydopyrine is a more powerful antipyretic and analgesic than others.

Nervous system.—Their action on the nervous system is not well understood. They however act as powerful **analgesics**, and though not strongly hypnotic, yet taken at bedtime they favour the onset and maintenance of normal sleep. The pain sensation is abolished and unlike opium they do this without any appreciable effect on the mental activity. It has been suggested that the analgesia is the result of an action on synapses in the pain conveying tract in the thalamus adjacent to the heat centre. Most of the antipyretics and notably acetanilide and phenazone increase motor excitability of the cord and cause convulsion, specially in frogs. How it is produced in mammals is not definitely known, possibly they are cerebral. When large doses are introduced into the blood directly the convulsions resemble those of strychnine inasmuch as they are spinal and are produced after separation of the cord from the brain. It has been suggested that they may be due to asphyxia and not to any direct effect on the brain. The peripheral nerves and the nerve-endings are not affected even in poisoning.

Elimination.—These drugs are rapidly absorbed and eliminated. Acetanilide and phenacetin are mainly converted into paramidophenol. They are excreted in the urine and disappear from the body within 24 hours.

Toxic action.—Large doses cause great prostration, sometimes vomiting, weak, irregular pulse, slow respiration and sweating. In toxic doses these symptoms are aggravated leading to profuse sweating, cyanosis, collapse and death. Sometimes a rash appears on the skin. Poisoning may occur from phenazone and acetanilide. The writer

had a case of poisoning from 30 grs of phenacetin. Cyanosis of the face, mostly of the lips, hands and feet, and a slight depression were the only prominent symptoms.

Treatment.—Warmth to the surface, stimulants, strychnine and atropine hypodermically, and oxygen inhalation.

Action of Phenazone and Phenacetin compared.—Phenazone is the best in respect of the efficacy, rapidity and certainty of its action, while phenacetin is safe, and its action more lasting, rarely producing subnormal temperature or collapse. Phenacetin has also a soothing and soporific action. Both of them cause profuse sweating *but do not shorten fever.*

THERAPEUTICS

Externally —Acetanilide and phenazone are occasionally used as a dusting powder, or as an ointment (20 grs. to 1 oz) for chronic ulcers and eczema. A 10 p c solution of phenazone locally applied stops epistaxis.

Internally.—As antipyretics all these drugs are used to reduce fever heat, but phenacetin, being the safest, is prescribed more frequently. They take about two hours to bring down the temperature, but phenazone and acetanilide do it more rapidly. To maintain the reduced temperature they require to be repeated every 4 hours, and this sometimes leads to dangerous symptoms on account of their depressing influence on the heart. They cannot control the duration of fever, for as soon as the effects are over the fever rushes up again. Hence many physicians are averse to using them as antipyretics as a routine treatment, but they are very useful agents in cases where the temperature is so high as to endanger life, where the high temperature is the chief cause of distress, and where reduction of temperature and increased comfort are not counterbalanced by their masking the true condition of the disease. A more serious objection to the use of these drugs is that the course of the disease may be obscured as the natural daily variation of temperature which often guide the physician regarding the course of the disease and its severity is masked making diagnosis and prognosis more difficult. In hyperpyrexia they cannot be relied upon. Both phenazone and phenacetin have been given in every form of febrile condition with a high temperature such as typhoid, remittent, intermittent, puerperal fever, etc., but with unsatisfactory results. In fact one should not use drugs which act on the heat regulating mechanism, but should rely, for the reduction of temperature, upon those means which promote the dissipation of heat without influencing the centre.

A very important use of these drugs depends upon their valuable property of relieving certain types of pain chiefly of neuralgic character. As **analgesics** therefore these drugs

are largely used to relieve pain. For reasons already stated, phenacetin and amidopyrine will have the preference. There is hardly any pain which cannot be alleviated by phenazone. 5 to 10 grs. given hourly for 3 or 4 doses act like a charm in almost every form of headache and migraine. Phenacetin does it equally well in 5 gr. doses. Moreover, the pains of ataxy, sciatica, angina, internal aneurism, dysmenorrhœa are soon cut short by these drugs. These drugs are often used in preference to morphine because of its liability to produce a habit. They are of little value in pains of a spasmodic nature, for instance renal colic, when morphine is the drug of choice.

Phenacetin in 1 gr. doses is a useful hypnotic in the febrile diseases of children.

As a nervine sedative, phenazone is occasionally used in epilepsy, chorea, nocturnal emissions, laryngismus stridulus, asthma, sea-sickness, enuresis, etc. Antipyrin has been used in whooping cough, and is often combined with belladonna when it gives relief by not only lessening the severity of the attacks but by actually shortening the course of the disease.

Untoward effects.—Sometimes evidence of toxic manifestations are noticed following the use of antipyrin. These are chiefly due to idiosyncrasy. They are (1) urticarial rash, erythematous or bullous eruptions with or without œdema of the skin, mucous membrane and glottis; (2) gastric intolerance, avoided by combining with alkalis; (3) profuse perspiration, subnormal temperature and a tendency to collapse, specially in tubercular and cachectic patients; (4) cyanosis, fall of blood-pressure and intermittent pulse; (5) albuminuria, specially after long continued use.

Recently a condition known as agranulocytosis from the use of amidopyrine has been recorded. This is characterised by severe leucopenia, ulcerative angina, prostration followed by death. Other drugs, notably, gold and organic arsenic compounds have also been found to produce this effect.

Prescribing hints —All these may be given in powders, cachets or capsules. Phenazone being soluble in water can be given in peppermint water which disguises its taste, while the others can be suspended by compound tragacanth powder. Sometimes they may be given with advantage in brandy or whisky. Acetanilide is not so much used nowadays because of its liability to toxic effects. As a rule phenazone and amidopyrine do not produce any side effects although the latter drug has been known to produce agranulocytosis, a rare but fatal condition, which has reduced the popularity of this drug. The student should remember that calomel when triturated with antipyrin forms a toxic compound, and with chloral and sodium salicylate form oily liquids. The solubility of the salts of quinine and caffeine

is increased by the addition of antipyrin. On account of a long list of incompatibles phenazone is better given alone

ANTISEPTICS AND ANTIRHEUMATICS

ACI U SALICYLICU

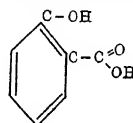
Salicylic Acid. (Acid Salicyl.)

Source—May be obtained by the interaction of sodium phenate and carbon dioxide. Contains not less than 99.5 p.c. of $C_6H_5O_3$.

Characters.—Colourless crystals, or a light feathery crystalline powder, almost odourless; taste, sweetish and acrid. *Solubility*—1 in 500 of water, 1 in 3.5 parts of alcohol (90 p.c.), readily in ether.

Incompatibles.—Iron salts, quinine sulphate, sp. æther. nitrosi, and sp. ammon. aromat.

B.P. Dose—5 to 10 grs. or 0.3 to 0.6 gm.



OFFICIAL PREPARATION

1. Unguentum Acidi Salicylici.—2 p.c.

S II SALICYLAS

(Sod. Salicyl.)

Sodium Salicylate. $NaC_7H_5O_3$

Source.—Obtained by the interaction of salicylic acid and sodium carbonate. It contains not less than 99.5 p.c. of pure sodium salicylate.

Characters.—Colourless, small crystals or crystalline flakes, or a white powder; odourless, or with a faint characteristic odour; taste, sweetish, saline, unpleasant. *Solubility*.—1 in 1 of water, 1 in 6 of alcohol (90 p.c.).

Incompatibles.—Acids, antipyrin, quinine and iron salts.

B.P. Dose—10 to 30 grs. or 0.6 to 2 gm.

ACI U ACETYLSALICYLICU

(Acid. Acetylsalicyl.)

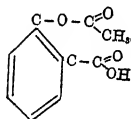
Acetylsalicylic Acid. $C_9H_8O_4$

Syn.—Aspirin.

Source.—Obtained by the action of acetic anhydride or of acetyl chloride on salicylic acid. Contains not less than 99.5 p.c. of $C_9H_8O_4$.

Characters.—Small, colourless, acicular crystals, or a white crystalline powder. Odourless; taste, slightly acid. Stable in dry air, but in contact with moisture gradually hydrolyses into acetic and salicylic acids. *Soluble* in 300 parts of water, in 5 parts of alcohol (90 p.c.), and strong solution of ammonium acetate.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 gm.



NON-OFFICIAL PREPARATIONS AND DERIVATIVES OF SALICYLIC ACID

1 **Ammonii Salicylas**, U.S.P.—In colourless, lustrous prisms or plates, or a white crystalline powder. Taste, slightly saline and bitter, afterwards sweetish. No odour. *Dose*, U.S.P.—15 grs. or 1 gm.

2 **Calcii Acetylsalicylas** *Syn. Tylicalsin*—White amorphous, non-hygroscopic

copie powder Soluble 1 in 6 of water but dissociates in solution *Dose* —5 to 15 gis. or 0.3 to 1 gm *Antirheumatic and influenza specific* Combines the good effects of sodium salicylate and aspirin

3 **Ferri Salicylas**—Antiseptic, astringent *Dose* —3 to 10 gis or 0.2 to 0.6 gm

4 **Colloidium Salicylicum Co., B P C** *Syn*—*Corn Paint*—Salicylic Acid 12, Extract of Indian Hemp 2, Acetone 30, Acetone Collodion to 100 A painless solvent for hard and soft corneal

5. **Injectio Sodii Salicylatis.**—1 in 20 of sterile water. Injected into the seat of pain in *rheumatism* *Dose* —15 to 30 ms or 1 to 2 c c.

6 **Salacetol** *Syn.*—*Acetyl methyl-salicylate*—A compound obtained by heating monochloro-acetone and sodium salicylate As an intestinal antiseptic in diarrhoea *Dose* —10 to 30 gis or 0.6 to 2 gm in cachets or suspended.

7 **Salophen.** *Syn.*—*Acetyl-para-amidosalol*—Whitish, tasteless crystals, insoluble in water Has a quicker action in acute rheumatism than salicylic acid *Dose* —5 to 15 gis or 0.3 to 1 gm in cachets

8 **Aspirodine** *Syn.*—*Acetyl Iodo-salicylic Acid*—Contains 41 p c iodine Embodies the properties of iodides and aspirin. Useful in *rheumatic affections, arteriosclerosis, asthma, scrofula and enlarged glands* *Dose* —5 gis. or 0.3 gm daily after food

9. **Sedaspirin** *Syn.*—*Acetyl Bromo-salicylic Acid*—A stable compound with 31 p c bromine Combines the sedative action of bromides *Dose* —5 to 10 gis. or 0.3 to 0.6 gm.

SALICINU

Salicin. (Salicin.). $C_{13}H_{18}O_7$

Source.—A glucoside obtained from the bark of various species of *Salix*, and of *Populus*.

Characters.—Colourless crystals, or white crystalline powder. Taste, bitter. *Solubility.*—1 in 28 of water, 1 in 80 of alcohol (90 p.c.), insoluble in ether.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 gm.

PHARMACOLOGY

Externally.—Salicylic acid and salicin are antiseptics, but the acid is the more powerful. A 2 p.c. solution of the acid kills bacteria and checks fermentation, but its salts have no antiseptic properties. Salicylic acid is a powerful local anhydrotic. Applied to the nose it causes sneezing and cough. It has special action on the epithelium and in dilute form the acid acts as a keratoplastic agent, and aids regeneration of new epithelium. In a concentrated form it acts peculiarly on the epidermis specially the corneous layer, and the horny cells are softened, gradually loosened and separated without much inflammatory reaction.

Internally Alimentary canal.—Salicylic acid is an irritant to the stomach, and when taken undiluted causes pain, nausea and vomiting. Vomiting in cases of poisoning is a central effect. Sodium salicylate and salicin are less irritant. Salicin is a bitter, stomachic. Salicin is transmitted unchanged into the intestine, where it is broken up probably by the help of the pancreatic juice into saligenin and glucose, and saligenin again into salicyluric, salicylous and salicylic acid. Acid acetylsalicylic passes through the stomach unchanged

and therefore does not act as an irritant here, but is decomposed partly into salicylic acid in the gut and is absorbed as sodium acetylsalicylate.

Blood.—Salicylic acid enters the blood as sodium salicylate, which, at any rate, is the form in which it is found in the blood. Some think that it exists as an albuminate, but of this there is no proof. It is possible that sodium salicylate is converted again into salicylic acid by carbonic acid in the inflamed joints. However, the fact remains that a portion of the salicylic acid of the salicylate unites with glycocoll either in the blood or tissues to form salicyluric acid; thus $\text{HC}_7\text{H}_5\text{O}_3$ (salicylic acid) + $\text{C}_2\text{H}_5\text{NO}_2$ (glycocoll) = $\text{HC}_7\text{H}_5\text{NO}_4$ (salicyluric acid) + H_2O . This chemical change is identical with what happens in the conversion of benzoic acid into hippuric acid.

Heart and blood-vessels.—In therapeutic doses salicylic acid, sodium salicylate and salicin have very little effect on circulation. Very large doses make the heart slow and weak, the muscles get relaxed and dilated causing a fall of pressure. The idea that they depress the heart was based on observations made with artificial preparation which occasionally contained orthocresotic acid, a powerful cardiac depressant. Physiologically pure artificial salt is not depressant.

Temperature.—The salicylates in moderate doses reduce febrile temperature, due to increased heat dissipation from cutaneous dilatation, aided by perspiration. In healthy individuals this is compensated by increased heat production, so that the normal temperature is not easily affected. They are therefore antipyretics. A single dose of 20 to 30 grs. of sodium salicylate may bring down the temperature of 105°F . to 101°F . in 2 or 3 hours.

Skin.—Salicylic acid, aspirin and sodium salicylate increase perspiration due to (1) dilatation of the cutaneous vessels, and (2) according to Cushny to increased activity of the sweat centre. Dilatation of the skin vessels may cause some skin rashes to appear.

Liver.—The salicylates are efficient biliary antiseptics. They increase the secretion of bile, possibly from some specific action on the liver cells. The bile is rendered thin and watery. There is however a total increase in the solids of the bile. In this respect the action of sodium salicylate resembles that of sodium benzoate.

Nervous system.—Their action on the nervous system is ill-understood. They produce a train of symptoms identical with cinchonism (*see* salicylism).

etabolis .—It increases the elimination of nitrogen and sulphur showing destruction of proteins. Excretion of uric acid is increased up to 100 p.c. even in purin free diet. Due to increase of fixed acid and lowering of reserve alkalies

combined with defective excretion due to damaged kidneys it causes **non-gaseous acidosis**.

Kidneys.—Secretion of urine is increased to some extent possibly due to its direct action on the renal cells. Salicylic acid is excreted in the urine as salicyluric acid and sodium salicylate. It can be detected in the urine within 10 to 30 minutes after ingestion. It sometimes causes nephritis with bloody and albuminous urine. Large doses increase the excretion of urea and uric acid, and give sometimes to the urine greenish colour due to the presence of pyrocatechin. It renders the urine **antiseptic** and **increases its acidity**. The urine of patients taking salicylic acid gives a purple colour on the addition of solution of ferric chloride.

Uterus—Some think that salicylic acid is an **emmenagogue** and causes abortion, but there is no sufficient evidence to confirm this statement.

Elimination—Salicylates are excreted to some extent in all the secretions, chiefly by the urine, and to a less extent by the sweat, saliva, bile, sputum and fæces. The excretion begins within 15 minutes and is practically completed in 6 to 8 hours. The rapid excretion explains the necessity of large and repeated doses.

Aspirin is about one and one-half times more toxic than sodium salicylate. Even small doses (5 to 10 grs.) occasionally produce alarming symptoms. It is however a stronger analgesic and antipyretic due to the undecomposed acetyl compound entering the nerve cells more rapidly.

Toxic action.—Mild toxic symptoms may appear when cases of rheumatic fever are treated with large doses of salicylates. The symptoms resemble cinchonism, buzzing in the ears, disturbed hearing and vision, headache, vertigo, mental confusion from disturbance of circulation of the brain are the early symptoms. When these appear further use of the drug should be stopped. If however it is pushed further, nausea, vomiting, deafness, delirium, flushed face, free perspiration, rapid pulse, deep and accelerated respiration and air hunger may be present.

The disorders of hearing have been ascribed to congestion of the tympanum, although some attribute it to the same causes as in quinine, i.e. changes in the nerve cells in the ear. Similarly the impairment of sight is due to vascular and retinal changes in the eye.

All the symptoms of salicylism have been attributed to a marked disturbance in acid-base equilibrium and formation of **non-gaseous acidosis** and does not occur when the drug is used with sufficient alkali. This acidosis is the result of increased production of acids combined with defective excretion due to a damaged kidney.

THERAPEUTICS

Externally.—Salicylic acid is largely employed in surgical practice in the form of a lotion, ointment, lint, cotton, etc. Small epitheliomas and chancres soon heal when pure acid is daily dusted over them. In lupus, corns and tylosis collo-dium salicylicum is a useful application. A hot strong solution is recommended in acne, and an ointment containing

30 grs. each of phenol and salicylic acid in 1 oz. cures ringworm. Being non-volatile it is not an effective antiseptic for deep suppurating wounds. Salicylic acid and talc powder is an excellent application for checking excessive sweating in phthisis, and fetid perspiration of the feet and armpits. A 1 to 4 p.c. solution or the ointment often checks the itching of eczema, intertrigo and urticaria. Salicylate of soda is also used by ionisation in cases of fibrositis.

Internally.—Salicylic acid is locally applied to diphtheritic membranes. It is used as an internal antiseptic in sarcinous vomiting and fermentative dyspepsia.

As an *antirheumatic*, salicylic acid and the salicylates are considered specifics for **acute rheumatism**, possibly by the setting free of salicylic acid in the inflamed part by the carbonic acid in it. They reduce the temperature, lessen the swelling, and relieve the pain, if 20 to 30 grains are given every 2 hours, until about six doses are taken, and then at longer intervals. This specific action is produced only when the body is saturated with the salicylate, and the action remains as long as this saturation is maintained. Once however the urgent symptoms are relieved the dose may be reduced, but it has to be used for a prolonged period. If the dose is reduced too much the symptoms return again. Even after an apparent cure the treatment should be continued for one or two weeks. The liability to cardiac complications is minimised by salicylic acid treatment, although some authorities aver that the tendency to both endocarditis and pericarditis is greatly increased by the use of salicylates in acute rheumatic fever. Experience has shown that the cardiac complications are less if the patient is kept in bed for a long time, which also minimises any risk of permanent damage to the heart. Sodium salicylate may also be used as subcutaneous or intravenous injection or directly into the inflamed joint. The intravenous route is safe and painless and is best suited for cases where the drug is not well tolerated when given by the mouth or causes no improvement. The following solution may be used, *viz.*—sodium salicylate (pure) 120 grs. or 8 gm. in freshly sterilised distilled water $1\frac{1}{2}$ oz. or 50 c.c. Of this 2 c.c. is injected once or twice a day. If necessary 30 grs. or 2 gm. of caffeine sodium benzoate may be added to the above solution. In the hyperpyrexia of rheumatism salicylates are of no use. In chronic rheumatoid arthritis, gout, gonorrhœal rheumatism, opinions differ as to their utility. As an antirheumatic aspirin is inferior to the salicylates, but is frequently of some value in chronic cases, since it is usually better borne and is probably more slowly eliminated.

As an *antipyretic*, sodium salicylate and salicin may be usefully employed in typhoid, remittent, intermittent and inflammatory or specific fevers. Sodium salicylate 3 grs

given hourly gives good results in quinsy. Aspirin is more freely used in the form of tablets for colds, sorethroat, headache and influenza.

Intravenous injection of sodium salicylate has been used with success in psoriasis (10 c.c. of a 20 p.c. solution) given three times a week for 4 to 5 weeks, and in encephalitis lethargica.

As a *sclerosing agent* its use has been highly recommended in the injection treatment of varicose veins. For this 3 c.c. of a 20 p.c. solution is injected into the vein, the varices being first made empty of blood. One injection generally suffices, but if necessary this is followed, a week later, by another injection of 30 p.c. solution. If combined with 10 p.c. sodium chloride these injections are practically painless. Great care should be taken in giving these injections since any leakage into the surrounding tissue may cause sloughing.

As a *hepatic stimulant*, all these drugs may be given in torpidity of the liver and catarrhal jaundice, but sodium salicylate is the most effective. Sodium salicylate and aspirin are both useful in the treatment of hepatic colic, and are given with benefit as solvents of gall-stones.

As an *analgesic*, sodium salicylate may be given in neuralgias and lumbago, and is considered to be an effective remedy for sciatica. In chronic sciatica it gives the best result when combined with iodide. It has been extolled in chorea, but it seems that unless associated with an attack of rheumatism, recent or remote, it has no specific action in this disease. As an analgesic aspirin is superior to sodium salicylate and resembles the drugs of the phenacetin group, and is used to relieve pain of diverse nature in preference to sodium salicylate. Because of its greater solubility, calcium acetylsalicylas is more easily absorbed and is better borne causing less renal irritation.

Salicylate sometimes helps absorption of effused fluid and has been used in the treatment of pleurisy. How it helps this is not understood and the little diuresis which follows its use will not explain the mechanism of its action.

Sodium salicylate and aspirin have been found to reduce the quantity of sugar in the urine in diabetes.

Prescribing hints.—Sodium salicylate is best given in solution. If mixed with ammonia the mixture gradually turns from pale-yellow to brown on exposure to air. When given with quinine or citric acid, precipitation occurs. Theoretically aspirin should not be prescribed with bicarbonate of soda, but the bicarbonate lessens the nausea and heart-burn which sometimes result from its use. Aspirin is best administered in cachets, tablets or in powders. Alcoholic solutions decompose it to salicylic acid and acetic acid on standing. It may be given in milk to children.

On account of the rapid elimination the quantity required

should be divided into several doses and given every three or four hours. When treating cases of rheumatism with large doses, the salt should be freely diluted and combined with bicarbonate of soda to avoid irritation of the stomach and acidosis. The full dose should be continued for three days after subsidence of the pain and temperature, and then gradually reduced. The sweetish taste of sodium salicylate is unpleasant and nauseating to many patients. Bromides lessen the tendency to salicylism. It cannot be prescribed in an acid solution as salicylic acid is formed which is insoluble. Salicin is not freely soluble in water but the addition of glycerin increases its solubility. For application to joints methyl salicylate is generally used either undiluted or mixed with olive oil.

Caution.—The natural or the physiologically pure artificial salts are only to be used. They should be given with caution to children, old and weak individuals, and to persons suffering from cardiac and renal diseases. The administration of the drug is to be suspended if headache, deafness and ringing in the ears show themselves.

ETHYLIS SALICYLAS

Methyl Salicylate. (Methyl. Salicyl.). $C_8H_8O_3$

Syn—Artificial Oil of Wintergreen

Source—Obtained by the esterification of methyl alcohol and salicylic acid. Contains not less than 98 p c. of pure methyl salicylate

Characters.—A colourless, or pale yellow liquid. Characteristic, aromatic odour, taste, sweet, warm, aromatic. Slightly soluble in water, freely in alcohol (90 p c.) Sp. gr. 1.186 to 1.191

B P Dose—5 to 15 ms or 0.3 to 1 ml

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

1. **Linimentum Methylis Salicylatis, B P C**—Menthol 5, oil of eucalyptus 10, rectified oil of camphor 25, methyl salicylate to 100. As a paint over *rheumatic joints* and *neuralgic areas*, the parts being covered with oil silk

2. **Ung Methylis Salicylatis Co, B P C Syn.**—*Analgesic Balsam*—Methyl salicylate 50, menthol 10, eucalyptol and oil of cajuput (by wt) each 25, white beeswax 20, lanoline 15. In *sciatica*, *lumbago* and *rheumatism*

PHARMACOLOGY AND THERAPEUTICS

The action and uses of methyl salicylate are much the same as those of the salicylates. As it is absorbed by the unbroken skin it is used externally. It may also be used internally in capsules.

EN OINU

Benzoin. (Benzoin.)

Syn.—Gum Benjamin; Sumatra Benzoin. **Syn. I. V.**—*Loban*.

Source.—A balsamic resin obtained from the incised stem of *Styrax Benzoin*.

Characters.—In hard, brittle masses consisting of whitish or reddish tears embedded in a greyish-brown or reddish-brown translucent matrix. Odour agreeable; taste, slightly acrid. When heated it melts and evolves whitish fumes with an irritating odour.

Composition.—(1) *Benzoic acid* 18 p.c. (2) *Cinnamic acid* 20 p.c. (3) *Volatile Oil*. (4) *Resins*.

OFFICIAL PREPARATION

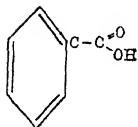
1. *Tinctura Benzoini Composita*. *Syn.*—*Friar's Balsam*.—B.P.
Dose.—30 to 60 ms or 2 to 4 mils.

ACID BENZOICUM

Benzoic Acid. (Acid. Benz.). $C_7H_6O_2$

Source.—Obtained from benzoin, or prepared synthetically.

Characters.—In light feathery, colourless and odourless crystals. Melts and sublimes on heating. *Solubility*—1 in 450 parts of water, 1 in 3 of alcohol (90 p.c.), freely in chloroform and ether.



Incompatibles—Ferric salts and mercuric chloride.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 gm.

Enters into.—Tinct. Opii Camphorata.

SODIUM BENZOAS

Sodium Benzoate. (Sod. Benz.). $NaC_7H_5O_2$

Source and characters.—Prepared by neutralising benzoic acid with sodium carbonate. A white, amorphous, granular or crystalline powder with a faint benzoin odour. Taste, unpleasant, sweetish and saline. *Solubility*.—1 in 2 parts of water, slightly in alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES OF BENZOIC ACID

1. *Cryogenine* *Syn.*—*Meta-benzamine semicarbazide*.—A crystalline body sparingly soluble in water, used in *pyrexia of phthisis* and *enteric fever*. Has no depressing action. Dose—3 to 24 grs or 0.2 to 1.5 gm.

2. *Sodi Hippuras*.—A soluble white amorphous powder. A solvent of urates in *gout* and *gravel*, and to lower *blood-pressure*. Dose—5 to 30 grs or 0.3 to 2 gm.

3. *Benzyls Benzoas* *Syn.*—*Spasmodin*.—An ester of benzyl alcohol and benzoic acid. Used in diarrhoea and dysentery, intestinal, renal and biliary colic, spastic constipation and any spasmodic condition. Dose—5 to 8 ms. or 0.3 to 0.5 ml of 1 in 5 alcoholic solution in water or emulsion.

PHARMACOLOGY

Externally.—Both benzoin and benzoic acid are antiseptics. A concentrated solution is a local stimulant and irritant.

Internally. **Gastro-intestinal tract and liver**.—The salts are less irritant and are therefore used in preference to the acid. In small doses they have little effect on the stomach and intestine, but in large doses irritate them. They are hepatic stimulants increasing both the quantity and solids of the bile. The acid is an intestinal disinfectant.

Respiratory tract.—Both the gum and the acid cause sneezing when inhaled. Their vapour directly stimulates the bronchial secretion which is also remotely stimulated during their excretion when given by the mouth. Hence they are expectorants. They also disinfect the secretion.

Urinary tract—Benzoic acid and its salts are largely excreted with the urine, partly unchanged, but chiefly as hippuric acid. Occasionally succinic acid also appears in the urine. The appearance of hippuric acid in the urine is due to the decomposition of benzoic acid in the presence of glycocoll in the renal cells but not in the blood. Hippuric acid thus formed performs most important functions. It stimulates the activity of the renal cells and renders the alkaline urine acid. Hence benzoic acid and benzoates are diuretics and acidifiers of alkaline urine. Over the mucous membrane of the urinary tract they have a soothing and disinfecting influence.

Temperature.—Benzoic acid and benzoates are antipyretics sometimes acting more powerfully than salicylic acid, but how they act is not known.

Metabolism.—They increase metabolism and there is excess of nitrogenous constituents of urine, and the body weight falls. Benzoic acid reduces the excretion of uric acid.

Elimination.—Chiefly with the urine, and partly with the sweat, saliva and bronchial secretion, which are stimulated to a slight extent.

THERAPEUTICS

Externally—A piece of lint soaked in Friar's balsam may be used to stop bleeding from, and promote the healing of, fresh wounds. In the same manner it may be used as an effective dressing for ulcers of all sorts. Undiluted Friar's balsam injected into sinuses establishes a healthier action in these tracts and heals them quickly. Locally applied, it relieves the pruritus of urticaria, and in solution (5 p.c. of the compound tincture with 5 p.c. of glycerin in water) it is a soothing stimulant application for the skin after the cure of acne. Benzoin is mixed with lard to prevent its decomposition, but it occasionally causes irritation of the skin.

Internally. **Lungs**—Both benzoin and benzoates are largely employed either by the mouth or as an inhalation, in chronic bronchitis and phthisis, particularly if the expectoration is foul and scanty. The vapour of the tincture has been found to cut short, with surprising rapidity, attacks of catarrh and influenza.

Urinary tract.—As an *acidifier* of alkaline decomposing urine in cystitis or pyelitis, and in phosphatic calculi, benzoic acid and benzoates have been used, but they have been replaced by acid sodium phosphate which is more powerful in acidifying alkaline urine, and by hexamine or mandelic acid which are better and more powerful urinary antiseptics. The salts should be used in preference to the acid, as they cause less gastro-intestinal irritation. They may be combined with urinary sedatives, such as tincture of hyoscyamus.

Rheumatism and gout.—Benzoate of soda may be given in acute rheumatism when salicylate of sodium cannot be borne or fails to do good. In gout it is occasionally used with the idea that it converts uric acid into hippuric acid and thus helps its elimination.

Prescribing hints.—The acid may be given in cachets, pills, or mixture suspended by mucilage. With acids the benzoates are decomposed into insoluble benzoic acid, and with ferric salts form insoluble flesh coloured ferric benzoate. They are also incompatible with lead, silver and mercury. Most alkaloids form insoluble benzoates. The vapour may be inhaled through an inhaler or even directly from a bottle.

GROUP XVI

CHEMOTHERAPEUTIC AGENTS

Before proceeding with the discussion of the individual drugs of this group it is necessary to describe the Reticulo-endothelial System, which modern research has shown to influence the action of drugs in the treatment of different infectious diseases. Evidence is accumulating in favour of the view that drugs, which are supposed to have a specific action, in the majority of instances, act in an indirect way through the different tissues of the body particularly through the cells of the reticulo-endothelial system. Many drugs act as specifics within the body of the host while possessing little or no such effect outside the body. Moreover, certain drugs are rapidly eliminated by the body, and in dilutions in which they occur in the blood and tissues after the administration in therapeutic doses, it is impossible to exert any direct action on the parasites. In fact it has been shown (see page 66) that the co-operation of the host is an important factor in the production of the specific action of a drug. It has therefore been suggested that this system is responsible for the formation of the natural defensive mechanism, which is an important factor in the causation of cures in different infections, and dysfunction of this system by 'blockade' or splenectomy experiments reduces or even completely abolishes the therapeutic value of a drug.

The exact manner in which the system responds to the stimulus of the specific drug depends upon the nature of the infecting organism. While some parasites are rapidly destroyed by phagocytes, others require to be disposed of by the destructive action of the lytic antibodies. In the first instance the response is evidenced by mobilisation and functional activation of the phagocytic cells of the system, while in the case of the other there is increased antibody production. When both these methods are of little use, the system utilises other methods, one being the elaboration of a powerful parasitocidal substance from the drug used. The modern conception of the specific action of a drug is that it stimulates the natural processes of the body in the cure of disease by bringing about such changes, directly or indirectly, either on the parasite or its environment as would be conducive to the success of the natural processes at work.

The different ways in which this system helps drugs in acting as specifics are as follows:—

1. By acting as a store-house for the drug and elaborating it slowly as required, thus preventing its rapid escape from the body and ensuring continuous supply.
2. By carrying the medicament to the neighbourhood of the lesion where it is most needed.

3. By possibly forming new compounds with greater parasitocidal properties.

4. It is possible that the drug stimulates the system in the production of more pronounced and effective phagocytic action and formation of antibodies. In fact Krishnan* has definitely shown that the phagocytic power of the cells of this system is stimulated by quinine in the treatment of malaria which accounts for the cure of the disease.

The reticulo-endothelial system is composed of a special group of cells of mesenchymal origin and of the macrophage or large mononuclear type possessing the property of phagocytosis and intracellular digestion. These cells are found in the liver, spleen, bone-marrow and lymphatic glands, and to a greater or lesser degree in other parts of the body. The cells composing this system are of six types of which *monocytes* and *histiocytes* or *clasmatocytes* possess powerful phagocytic properties. Both in health and disease this system performs diverse important functions of which phagocytosis is perhaps the chief and most important one, and it is possible that most of its other functions more or less depend upon this property.

The different functions of the reticulo-endothelial system may be classified as follows:—

1. *Formation of bile pigment.*—It is now recognised that bile pigment is formed in all tissues in which reticulo-endothelial cells are present including Kupffer's cells in the liver, but not by the glandular cells of that organ.

2. *Destruction and regeneration of red cells.*—It has been shown that the cells of this system take up for purposes of destruction those red cells whose allotted span of life is over, or those that have become damaged as a result of some inflammatory processes, toxins or parasitic invasion. Along with destruction there is also regeneration, and these two processes go hand in hand so that the red cell count is maintained at a constant level. In fact this system supplies the stimulus for regeneration of red cells, and in the absence of such stimulus the bone-marrow fails to manufacture sufficient number of red cells to maintain the equilibrium.

3. *Iron metabolism.*—Closely related to the regeneration of the red cells is the property of this system to utilise the iron from the hæmoglobin and degenerated red cells for the formation of fresh red cells. This metal is stored in the liver and spleen by the reticulo-endothelial cells which is metabolised in the synthesis for the manufacture of hæmoglobin.

4. *Cholesterol metabolism.*—Experimental evidence goes to show that storage of cholesterol is another important function of this system.

5. *Phagocytosis of bacteria and particulate substances.*—Experimental observations have shown that this system has the property of engulfing different bacteria and other organisms, e.g. protozoa, and carry them to internal organs, like the spleen and liver, for purposes of destruction. In many infectious diseases these cells have been found to be actually loaded with different organisms in infected tissues. Apart from the destruction of different bacteria and other organisms there is enough evidence to show that these cells readily ingest substances like Indian ink particles, vital dyes, carbon, colloidal particles of arsenic, antimony, bismuth and mercury.

The drugs belonging to this group are largely used as specifics in certain protozoal and other diseases and may be classified as follows:—

Class A Drugs used in Malaria

Cinchona and its alkaloids, Plasmochin, Atebrin

* Krishnan, *Indian Journal of Medical Research* Oct. 2, 1933

442 PHARMACOLOGY AND THERAPEUTICS

Class B Drugs used in Syphilis

Mercury, Bismuth, Arsenic, Iodides

Class C Drugs used in Leishmaniasis

Antimony and its compounds

Class D Drugs used in Trypanosomiasis

Tryparsamide, Pentavalent compounds of Arsenic (atoxyl), Bayer 205

Class E, Drugs used in Amœbic infection

1. Ipecacuanha, Emetine, Emetine Bismuth-Iodide, Gavano (*see* page 310)

2 Certain Organic Arsenic Compounds Acetarsol, Carbarsone

3 Kurchi and its alkaloids

4 Oxyquinoline Derivatives and certain Dyes Chinofonium, Rivanol

Class F Drugs used in Bacterial invasions · Sulphanilamide and its derivatives

Class A: Antimalarial remedies

CINCHONA

Cinchona. (Cinchon.)

Syn.—Cinchonæ Rubræ Cortex; Red Peruvian Bark.

Source.—The dried bark of the cultivated trees of *Cinchona calisaya*, *Cinchona ledgeriana*, *Cinchona officinalis*, *Cinchona succirubra*, and of hybrids of either of the last two species with either of the first two. Contains not less than 6 p.c. of the total alkaloids of cinchona, of which not less than one-half consists of quinine and cinchonidine.

Characters.—In quilled or curved pieces, up to 30 cm. or more long; 2 to 6 mm thick; outer surface, grey or brownish-grey; rough from longitudinal ridges, transversely cracked and warty; inner surface brick-red, coarsely striated. Fracture, shortly fibrous. Powder, brownish or reddish-brown. Slight odour. Taste, bitter, somewhat astringent.

Composition.—A. *Four important alkaloids*.—(1) Quinine, as a hydrate. (2) Cinchonine. (3) Quinidine. (4) Cinchonidine. These alkaloids are bases and behave like alkalis. B. *Three acids*.—Quinic acid. (2) Quinovic Acid. (3) Quinotannic Acid. C. *One glucoside*.—Chinovin, which easily splits up into chinovic acid and glucose. *Cinchona red*. One volatile oil which gives the bark its smell.

Incompatibles.—Ammonia, lime water, metallic salts and gelatin.

B.P. Dose.—5 to 15 grs or 0.3 to 1 gm.

OFFICIAL PREPARATIONS

1 *Extractum Cinchonæ*—Contains 10 p.c. of the alkaloids, or $\frac{1}{2}$ gr. in 8 grs B.P. Dose—2 to 8 grs. or 0.12 to 0.5 gm.

2 *Extractum Cinchonæ Liquidum*.—Contains 5 p.c. w/v of the alkaloids of cinchona, or $\frac{1}{2}$ gr in 15 ms. B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

3 *Tinctura Cinchonæ*—Contains 1 p.c. w/v of the alkaloids of cinchona, or $\frac{1}{2}$ gr. in 60 ms. B.P. Dose—30 to 60 ms. or 2 to 4 mils.

4 *Tinctura Cinchonæ Composita*—Contains 0.5 p.c. w/v of the alkaloids of cinchona, or $\frac{1}{2}$ gr in 60 ms. B.P. Dose—30 to 60 ms. or 2 to 4 mils

NON-OFFICIAL PREPARATIONS

1 *Cinchona Febrifuge*.—Contains crystallisable quinine 7.40 p.c., cinchonine 18.58 p.c., cinchonidine 5.84 p.c., quinidine 22.83 p.c., uncrystallisable alkaloids, ash, etc. 43.35 Dose.—1 to 10 grs. or 0.06 to 0.6 gm

2 *Cinchonidine Sulphas*.—In colourless, silky crystals, soluble 1 in 100 of water. Dose—1 to 10 grs or 0.06 to 0.6 gm

3 **Cinchoninæ Sulphas**—The sulphate of an alkaloid obtained from several species of cinchona. In white lustrous prismatic crystals. Odourless with a bitter taste *Dose* —1 to 10 grs. or 0.06 to 0.6 gm

PHARMACOLOGY AND THERAPEUTICS

Internally.—Cinchona bark is an astringent, bitter tonic, a febrifuge and a mild antiperiodic, due to the alkaloids and other ingredients it contains. The crude bark irritates the stomach and bowels. It is often prescribed with other vegetable bitters during convalescence from an acute febrile attack, or along with quinine salts to increase their antiperiodic property. Combined with Spiritus Ammonię Aromaticus the compound tincture makes an excellent "Pick-me-up." It also checks the craving for strong drinks.

Owing to its high quinidine content cinchona febrifuge is specially valuable in benign tertian infection. But owing to the presence of cinchonidine it has the disadvantage of causing vomiting. It is best given two and a half hours after food in *cachets*, *tablets* or in *mixture* with citric acid. The vomiting may be checked by the previous use of 10 ms. of solution of adrenaline chloride. With cinchona febrifuge relapses are less, and given with alkalies some consider it more effective than quinine. But according to Sinton it gave 73.1 p.c. relapses in simple tertian infection. The consensus of opinion is that provided its composition is standardised, it is but little inferior to quinine both in the production of clinical and radical cure and is certainly cheaper. In order therefore to supply such a standardised preparation Totaquina has been introduced, which contains 70 p.c. of the total alkaloids of which not less than one-fifth is quinine. The strength of this preparation even varies, but it is fairly reliable.

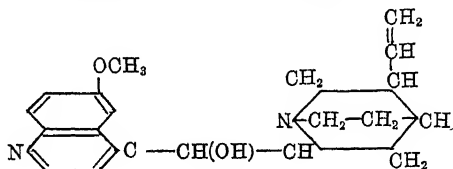
TOTAQUINA

Totaquine. (Totaquin.)

Source.—Is a mixture of alkaloids from the bark of *Chinchona succirubra*, *Cinchona robusta*, and other suitable species of *cinchona*. Contains not less than 70 p.c. of crystallisable cinchona alkaloids, of which not less than one fifth is quinine. Resembles cinchona febrifuge.

Characters.—A nearly colourless, or pale yellowish-grey, or pale brown powder; no odour; taste, bitter. Almost *insoluble* in water, almost completely soluble in warm alcohol (95 p.c.).

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 gm.



UININAE Y OC L I U

(Quinin. Hydrochlor.)

Quinine Hydrochloride. $C_{20}H_{24}N_2O_2 \cdot HCl \cdot 2H_2O$

Source.—Is the hydrochloride of an alkaloid, quinine, obtained from the bark of various species of *Cinchona*.

Characters.—Colourless, glistening needles; effloresces in warm air; no odour; taste, very bitter. *Solubility*.—1 in 32 of water, 1 in 2 of alcohol (90 p.c.).

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

UININA I Y C L RI U

(Quinin. Dihydrochlor.)

Quinine Dihydrochloride. $C_{20}H_{24}N_2O_2 \cdot 2HCl$

Syn.—Acid Quinine Hydrochloride.

Source.—Is the dihydrochloride of the alkaloid, quinine, obtained from the bark of various species of *cinchona*.

Characters.—A colourless powder; odourless; taste, very bitter. *Solubility*.—In 0.6 parts of water and in 12 parts of alcohol (90 p.c.). Reaction acid.

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.; 5 to 10 grs. or 0.3 to 0.6 grm. (intravenous or intramuscular injection).

UININAE SULP AS

(Quinin. Sulph.)

Quinine Sulphate. $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 7\frac{1}{2}H_2O$

Source.—The same as that of quinine hydrochloride.

Characters.—Colourless, glistening, silky needles; taste, intensely bitter. *Solubility*.—1 in 800 of water, giving the solution a bluish fluorescence; entirely in water acidulated with a mineral acid.

Incompatibles.—Alkalies and their carbonates, astringent infusions

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

OFFICIAL PREPARATIONS

1. *Liquor Quininae Ammoniatum*. Syn.—*Tinct. Quinin. Ammon.*—Contains 2 p.c. w/v of quinine sulphate and 1 p.c. w/v of ammonia, or 1 gr. in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

2. *Syrupus Ferri Phosphatis cum Quinina et Strychnina*. Syn.—*Easton's Syrup*. $\frac{1}{4}$ gr. quinin. in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

QUININAE ISULP AS

Quinine Bisulphas. (Quinin. Bisulph.)

Syn.—Quinine Acid Sulphate.

Source.—Bisulphate of an alkaloid, quinine, obtained from the bark of various species of *Cinchona*.

Characters.—Colourless, transparent or opaque, small needles. Odourless; taste, bitter. Becomes yellow when exposed to light. *Soluble* in 10 parts of water, in 23 parts of alcohol (90 p.c.). Solution strongly acid to litmus.

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

QUININAE ET AETHYLIS CAR ONAS

(Quinin. et Æthyl. Carb.)

Quinine Ethyl Carbonate**Syn.**—Euquinine. Tasteless Quinine.**Source.**—Prepared by the action of ethyl chlorocarbonate on quinine.**Characters.**—Fine, soft, white, matted needles; odourless; almost tasteless. Darkens on exposure to light. Slightly *soluble* in water, soluble in 2 parts of alcohol (90 p.c.), readily in dilute acids.**B.P. Dose.**— $1\frac{1}{2}$ to 15 grs. or 0.1 to 1 grm**QUININAE TANNAS**

(Quinin. Tann.)

Quinine Tannate**Source.**—A compound of tannic acid with an alkaloid, quinine, obtained from the bark of various species of *Cinchona*. Contains not less than 30 p.c. not more than 35 p.c. of anhydrous quinine**Characters.**—A pale-yellow, or yellowish-white, amorphous powder; taste, slightly bitter, astringent. Slightly *soluble* in water, soluble in alcohol (90 p.c.).**B.P. Dose.**— $1\frac{1}{2}$ to 15 grs. or 0.1 to 1 grm.**NON-OFFICIAL PREPARATIONS AND DERIVATIVES OF QUININE****1 Quinina, USP.**—An alkaloid obtained from the cinchona. In white micro-crystalline powder, odourless with a bitter taste. An alcoholic solution (1 in 10) is laevorotatory and alkaline to litmus. Insoluble in water. **Dose.** *USP*—15 grs. or 1 grm**2 Quininae Glycerophosphas**—In white crystalline powder. In obstinate *neuralgia*, or *chronic malaria*. **Dose.**—1 to 10 grs. or 0.06 to 0.6 grm**3. Quininae Hydrobromidum**—In white acicular crystals soluble 1 in 55 of water. With excess of diluted hydrobionic acid it lessens cinchonism. **Dose**—1 to 10 grs. or 0.06 to 0.6 grm**4 Quininae Dihydrobromidum, B.P.C.**—Yellowish crystals, very soluble in water. Used hypodermically. **Dose**—1 to 10 grs. or 0.06 to 0.6 grm. **Hypodermic**—3 to 5 grs. or 0.2 to 0.3 grm**5 Quininae et Urethani Hydrochloridum.**—Obtained by heating quinine hydrochloride 3; urethane 15, water 3. Used hypodermically and is non-irritant. In the *injection treatment of varicose veins* it is the drug of choice. **Dose**— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm**6. Quininae Lactas**—A crystalline or granular white powder soluble in 6 parts of water. Suitable for hypodermic use. **Dose**—1 to 5 grs. or 0.06 to 0.3 grm.**7 Quininae Salicylas.**—Silky crystals, sparingly soluble in water. In *remittent fever*, *rheumatism*, *neuralgia*, and *diarrhoea*. **Dose**—1 to 5 grs. or 0.06 to 0.3 grm**8. Quininae Acetylsalicylas.** **Syn.**—*Quinine Salacetate*.—In white crystalline powder, 64 p.c. of quinine. **Dose**—1 to 5 grs. or 0.06 to 0.3 grm**9 Quininae Valerianas.**—In *nervous headache* and *hysteria*. **Dose**—1 to 3 grs. or 0.06 to 0.2 grm.**10. Warburg's Tincture.** **Syn.**—*Tinctura Antiperiodica, B.P.C.*—Contains quinine sulphate about $4\frac{1}{2}$ grs. in 4 dis. **Dose**—1 to 4 dis. or 4 to 16 mls.**11. Aristochin.** **Syn.**—*Aristoquinine*.—The neutral carbonic ester of quinine in white tasteless powder containing 96 p.c. of quinine. Insoluble in water. **Dose**—1 to 10 grs. or 0.06 to 0.6 grm**PHARMACOLOGY****Externally.**—The characteristic action of quinine alkaloid is its effect on undifferentiated protoplasm, and it is an active

poison to many low forms of vegetable and animal life. Ciliary movements cease and according to Binz a solution of 1 in 20,000 destroys paramecia and amoeba. Spermatozoa and ova are destroyed by smaller strengths, and in strengths of 1 in 10,000 spirochaeta of vegetable decomposition become motionless, but those of relapsing fever are not influenced by strengths even of 1 in 500

While the sulphate and hydrochloride have a lethal action on paramecia, there can be no doubt that the newer quinidine and acridine derivatives have a remarkable effect as paramecial poisons and in destroying micro-organisms

Quinine salts and their derivatives have also a marked anaesthetic action with somewhat prolonged latent period, but the resulting anaesthesia is of longer duration. This anaesthetic action may be possibly due to the effect of quinine on the sensory nerve-endings or to the granular exudate formed at the site of injection which presses upon the nerve-endings

Internally. Mouth—It is a pure vegetable bitter, and has an intensely persistent bitter taste if taken in neutral or slightly acid solution, as the alkaline saliva precipitates the alkaloid. Like other bitters it reflexly stimulates the salivary secretion by exciting the gustatory nerves. The tannate is less bitter and the ethyl carbonate is almost tasteless

Stomach and intestine—All the cinchona alkaloids have a marked inhibitory effect on peptic and tryptic digestion. Cinchonine is the most powerful, hence this alkaloid cannot be tolerated for long when taken by the mouth. The monosalts inhibit peptic digestion still further as they use up most of the available free hydrochloric acid to form the more soluble disalts. For this reason only the bisulphate and dihydrochloride should be given when prescribed in the form of tablet by the mouth. Quinine for the most part passes through the stomach unchanged and reaches the duodenum, where the alkaline contents precipitate it as nascent alkaloid which is soluble in bile, and it is only in this form that quinine is absorbed. The absorption is retarded if it is given soon after or with meals. Three things are necessary for its absorption, *viz.* (a) solubility in the stomach; (b) alkalinity in the duodenum; and (c) available bile. The tannate and the ethyl carbonate are absorbed very slowly as they require to be hydrolised by the alkali of the duodenum.

In small doses (1 to 2 grs.) it is a bitter and stomachic, like calumba, and indirectly it acts as a general and cardiac tonic. In large doses (15 to 40 grs.) it produces the opposite effects—depression and gastro-intestinal irritation.

lood.—In whatever form quinine is given it circulates as quinine base and is present in the plasma, adsorbed on to the surface of the red blood-cells, but not within them.

Therefore those parasites that have become intracellular escape from its effect. After ingestion of a single dose of 20 grs of the sulphate the maximum concentration in the blood is 1 in 150,000 and after a single dose of 10 grs it is only 1 in 250,000. After absorption into the blood quinine has several specific actions which may be described under the following heads:—

1. *White corpuscles*.—After small doses of quinine there is some lymphocytosis, possibly due to contraction of the plain muscles of the spleen. After large doses this is followed by a reduction in the number of leucocytes, the lymphocytes being more reduced than the polymorphonuclears. This phase is again followed by leucocytosis, the polynuclear cells being only increased. In animals, not in man, quinine paralyses the movement of the white blood corpuscles. This may be seen by mixing a drop of the solution with a drop of fresh blood under a microscope. If quinine be injected into a blood vessel, it at once stops the emigration of the leucocytes; but it has no effect on the amœboid movements of those which have already passed out into the tissues.

2. *Red corpuscles*.—These are not materially affected, though many assert that it increases their number and causes an increase in their size. Hæmolysis occurs only when quinine circulates in the blood in sufficient concentration to cause arrest of the heart, *i.e.* 0.5 p.c. (Cushny).

3. *Hæmoglobin*.—The oxyhæmoglobin is made a stable compound, consequently the blood cannot either absorb or give up oxygen so readily as in health. Probably this does not occur in medicinal doses.

The malaria parasites.—The causal organisms of malaria belong to the genus *Plasmodium*, which belongs to the class of the protozoa known as sporozoa. Four species are generally recognised as being concerned in the production of human malaria, *viz.* *Plasmodium vivax*, the parasite of benign tertian malaria; *Plasmodium falciparum*, the parasite of malignant or subtertian malaria; *Plasmodium malarie*, the parasite of quartan malaria; and *Plasmodium ovale*, a parasite which produces a mild type of tertian malaria in Africa. In all forms of malaria the fever is as a rule quotidian at the beginning of a primary attack, but in the tertian forms it later occurs on alternate days, whilst in quartan it occurs every fourth day, *i.e.* two days intervene between each bout of pyrexia. Quinine 1 in 10,000 solution inhibits the amœboid movements of the plasmodium *in vitro*. Given by the mouth to infected man the plasmodium shrinks, becomes granular and finally disintegrates. Under quinine the parasites disappear from the peripheral circulation, when as the result of sporulation, the young parasites are set free in the blood plasma. A few of the more resistant type escape

and multiply and eventually provoke another paroxysm of fever. It is more effective on the young stages of the asexual parasites which are more susceptible to its effect while they are free in the blood plasma. After the parasites have entered the corpuscles they become resistant to quinine.

Quinine has no effect on sporozoites even in high concentrations, nor has it any action on the crescents and therefore mosquitoes can readily be infected even though the patient may be taking quinine. The exact manner in which it cures malaria is far from settled. In clinical attacks of malaria quinine has little or no action on the parasites until a febrile attack is imminent or has already occurred. The drug has no appreciable effect when given during the incubation period, and has little effect when given on the first or even on the second day of the initial fever. The drug is more effective after the patient has had several paroxysms and the parasites are beginning to decline as a result of natural defensive mechanism which human beings possess.* Since the drug is rapidly excreted it is difficult to accept any evidence of direct action on the plasmodia. In fact the concentration in the blood even when given in full doses does not exceed 1 in 100,000 and that this concentration does not kill the parasite *in vitro*. It has therefore been suggested that the action is indirect, and that the effective therapeutic agent may be a metabolite formed by the breakdown of the quinine in the tissue, though no evidence of such a metabolite has been traced. On the other hand Yorke and Macfie maintain that the real action depends upon the capacity of the host to form an immune body in response to the antigen formation resulting from the destruction of a large number of parasites by the medicament. The evidence in favour of the formation of an antibody is however rather meagre. Morgenroth believes that the parasites are unable to enter the red blood corpuscles which are made resistant against penetration thus making the parasites unable to multiply.

It is possible that several factors contribute towards the cure of malaria, the one that plays the predominant part is the capacity of the cells of the reticulo-endothelial system to respond to the stimulus of infection by mobilisation, proliferation and functional activation. Administration of quinine merely heightens these responses, and when they are adequate the disease is overcome. The factors such as the direct action of the drug on the parasite and infected red cells, as well as biochemical and other alterations in the serum, help to augment the efficiency of the phagocytic mechanism to varying extent. Krishnan summarises the mode of action of quinine as follows:—†

*Quarterly Bulletin of the Health Organisation of the League of Nations. June, 1933

† Krishnan, Indian Journal of Medical Research, October, 1933.

1. By accelerating the natural immune processes of mobilisation, proliferation and functional activation of the phagocytic large mononuclear cells composing the reticulo-endothelial system, the drug causes rapid engulfment and effective destruction of the parasites.

2. By bringing about an alteration in the electrical condition of parasites and infected red cells by direct action, it increases the susceptibility of these to phagocytosis.

3. By slowing down asexual reproduction and occasionally leading to the formation of sexual forms, it checks the intensity of infection.

4. By indirectly leading to the production of humoral changes (antibodies) and to the sensitisation of the cells of the reticulo-endothelial system it increases the resistance to infection.

5. By causing the removal of effete and old red cells and increasing the output of young red cells it renders the successful entry of parasites into these cells more difficult.

Heart and circulation.—Small doses reflexly stimulate the heart through the stomach, but large doses given intra-

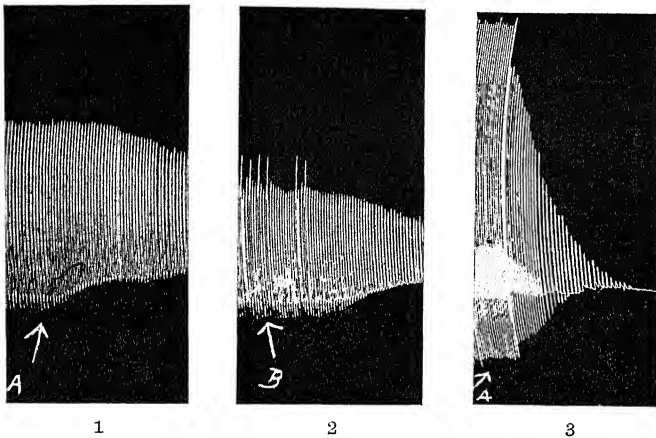


FIG 23.—Showing effect of Quinine on Isolated Rabbit's Heart perfused with Locke's solution.

1. Shows the effect of small dose; 2. shows the effect of a higher dose. Note more powerful depressant effect on the heart; 3. shows the effect of a large dose. Note the profound depressant effect making the contractions weaker and slower, and the heart eventually stops.

venously directly paralyse it; the pulse becomes slow and feeble, and at last the heart stops in diastole. These effects are not observed when quinine is given by the mouth even in large therapeutic doses and are due to direct action of the drug on the cardiac muscle. With weakness of the heart the blood-pressure falls. Intravenous injections cause a sharp and often dangerous fall of blood-pressure due to cardiac

weakness and peripheral vaso-dilatation due partly to central effect and partly to direct action on the muscle of the vessel. The dextrorotatory alkaloids of cinchona and quinidine cause greater fall of blood-pressure than their lævorotatory isomerides.

Respiration.—It is not affected by small doses, but is quickened by moderate doses, and in toxic doses it becomes slow and weak and then arrested. The gaseous interchanges are checked.

Liver and spleen—It has no action on the liver, but contracts the recently enlarged spleen rather by destroying the malarial parasite, and so preventing accumulation of the irritating products—pigments, etc., and reduces the hyperæmia.

Temperature.—Quinine has very little effect upon the temperature in health, but causes a marked reduction in fevers, particularly if they are of malarial origin. It is therefore an antipyretic in malaria. It sometimes lowers the temperature in fevers of non-malarial origin, but the precise mode of its action has not been definitely settled. It was formerly believed that this effect was due to its action on the metabolism. But the amount of quinine which lowers the temperature has no appreciable effect on the metabolism. It is possible that it acts on organisms other than malarial parasites. Its action is like other antipyretic drugs and is due to adjustment of the heat regulating centres, whereby there is increased heat loss from cutaneous vaso-dilatation and lessened heat production (*Hardikar*, 1925 and *Virchow*, 1927).

Metabolism.—Quinine and its derivatives were formerly believed to have a depressant effect on the metabolism. But observations made by *Hardikar* have failed to show any alteration in the protein metabolism either in man or in animals.

Nervous system.—Small doses have a tonic effect upon the nervous system, but large doses produce a train of symptoms known as cinchonism. Frequently there is impairment of the sense of hearing and perhaps of the sight. Ringing in the ears and slight deafness are noticed even after moderate doses. Sometimes there is complete loss of hearing, which disappears in a few days. Dimness of vision and sometimes total blindness may be present, and the patient may become colour blind. It has been thought that the ear symptoms are due to degenerative changes in the spiral ganglia of the cochlea.

The effects on the brain are not uniform. Some complain of fullness and heaviness of the head, while in others there is motor excitement with convulsion and delirium. Weakness of the heart and muscles, apathy, impairment of sight and hearing with unconsciousness and failure of respiration are observed in fatal cases.

Injected into animals it causes transient excitement of the central nervous system, but the real effect is depression. The cord is first stimulated and then depressed in mammals. The respiration first becomes quick but subsequently weak and slow, death occurs from respiratory failure. Tremors and convulsion before death are possibly due to asphyxia.

Uterus—Quinine occasionally acts as an *ecbolic* and it certainly intensifies the labour pains or re-establishes them if they are absent, when parturition has already commenced. Menstruation is sometimes induced by quinine in non-pregnant women. Metrorrhagia is an occasional symptom, although given after labour it often stops hæmorrhage.

Quinine in sufficient concentration causes contraction of uterine muscle in the non-pregnant uterus, *i.e.* after large doses. During pregnancy much depends on the state of the uterus. Large doses (15 to 30 grs.) cause increase in the *intermittent* uterine contractions, and in the presence of weak membranes, open the os and precipitate labour. Larger doses throw the uterus into a state of tonus. In malarial fever there is a greater danger from the fœtus dying as the result of the high temperature caused by the disease. So quinine must be given promptly and immediately, and as long as the doses are sufficiently small (2 to 5 grs. every few hours), and not more than 30 grs. are given during the course of twenty-four hours, there is no danger of *ecbolic* action of this alkaloid.

Absorption and elimination.—Quinine is absorbed by the duodenum and circulates in the blood as quinine base. Soluble salts are absorbed more quickly, but the rate of absorption varies in different people. Given in solution it appears in the urine very quickly. Quinine however does not circulate in the blood for a long time in any concentration; after an intravenous injection about 90 p.c. disappears within a minute. Excretion of quinine varies greatly in individuals and day by day. It may be detected in the urine half an hour after administration, and excretion may go on for 48 hours. Probably only about half the quinine administered is excreted by the urine, and according to Ramsden some of it is destroyed by the liver and kidneys. Any that is stored in the body will probably be found in the suprarenal bodies and the spleen, which organs are incapable of destroying it. Administered per rectum absorption is poor, irregular and unreliable, and may irritate the mucous membrane.

Toleration.—Some persons are very susceptible to the action of this drug. When a small dose produces headache and ringing in the ears, it is due to *idiosyncrasy*. The writer had seen a woman who became collapsed after taking 5 grs. of quinine sulphate.

The role of quinine in the production of black water has

not yet been definitely settled. A case of death following the administration of fifteen grains of quinine has recently been reported, the symptoms leading to this result being profuse internal and external hæmorrhage. A case recently occurred when intense urticaria followed the administration of the soluble hydrochloride, later of euquinine, but not of aristochin under which recovery ensued.

THERAPEUTICS

Externally.—Quinine cannot be freely used on account of its cost, though it is a *powerful antiseptic*. A lotion (2 to 4 grs. in 1 oz. of water) has been found very efficacious in diphtheritic conjunctivitis, and as an injection in hay fever, otorrhœa, and chronic cystitis.

Internally.—As an *antiseptic* it may be used as a gargle in stomatitis, diphtheritic ulceration and sore-throat.

As a *stomachic tonic* it is very useful in convalescence from an acute illness, particularly malarial fever. Its efficacy is considerably increased if it is combined with mineral acids and other bitters.

As an *antipyretic* it is far inferior to phenazone, phenacetin, or sodium salicylate, but there are many who advocate its use in typhus, typhoid and puerperal fever, acute rheumatism, insolation and pyæmia. It must be given just before the natural defervescence. It is useless in hyperpyrexia.

As an *antipyretic* and *febrifuge* it is considered a specific for malaria and all malarial intermittent and remittent affections

(1) *Malaria.*—Quinine acts as a specific in malaria, and a single dose of 10 grs. or two doses of 10 grs. every two or three hours should be given at least two hours before the expected paroxysm. It will then be absorbed into the blood in sufficient concentration before sporulation takes place, and thus will quickly attack the young spores, when they are free in the plasma and before they are able to enter the red blood corpuscles. It is probable that during this stage these asexual parasites are most susceptible to the effect of quinine. Whenever convenient this method should be followed. Sometimes, however, it is not possible to give sufficient quinine before the next paroxysm. In such cases it should be started when the temperature begins to fall so that a total quantity of 20 to 25 grs. in two or three doses can be given before the expected paroxysm. In every case the physician should be guided by the severity of the case, and quinine should be given at once without any reference to temperature in all cases of malignant infection or when there is danger of waiting for the temperature to fall

Whenever possible quinine should be given after the bowels have been opened, preferably by a dose of calomel and a saline. But this should be regarded as a matter of conveni-

ence and not of routine and no time should be lost in giving quinine once the case is diagnosed as of malaria. After the first or second dose, the question of giving a purgative may be considered.

To give large doses of quinine indiscriminately in all cases of malaria is a grave error. In fact relapses are more readily controlled by quinine than are the primary attacks. The treatment requires to be stopped after five to seven days in acute attacks, and if the patient has a recrudescence, then it should be given again for the same period or until the symptoms or the parasites disappear. It should not be used during the period the patient's blood is parasite-free. The tendency in the past had been to give too much quinine and to prolong the period of treatment unnecessarily. It should be noted that relapses are more common with benign tertian infection than the malignant one, which if properly treated rarely causes relapse. Relapses however are more common when quinine is not used for sufficient length of time and the natural power of resistance of the body has not developed. It is therefore necessary that quinine and iron should be given to improve the condition of the blood and general health*.

The routine treatment followed by the writer is to give 10 grs. of quinine with $2\frac{1}{2}$ grs. of acid acetylsalicylic in cachets as the first dose when the temperature is beginning to fall, followed by two more doses every three hours; the second and the third doses contain $7\frac{1}{2}$ grs. of quinine instead of 10 grs. If the paroxysm is not checked the treatment is repeated the next day but the second dose should contain 10 grs. of quinine. This usually checks the fever and the same procedure is followed for three to four days after the temperature has become normal. If no more attacks occur the use of quinine should be stopped for at least one week as it is no use giving this drug during the fever-free and parasite-free period. The writer is satisfied with this treatment and rarely had relapses. The success depends upon giving enough quinine, *i.e.* not less than 20 to 30 grs. within four to six hours, so that it will be absorbed and circulate in the blood in sufficient concentration when the parasites are free in the blood and before the appearance of the expected paroxysm, so that the parasites will be killed and thus prevent another cycle of development. Besides relieving

*R

Acid hydrochlor dil.	ms	10
Ferri et quinin cit	grs	10
Liq arsen	ms	3
Tinct nuc vom	ms.	$7\frac{1}{2}$
Mag. sulph	grs.	60
Glycerin.	ms	20
Aq. menth pip dest	ad oz	1

R

Quinin. hydrochlor	grs	$7\frac{1}{2}$
Acid acetylsalicyl	grs	$2\frac{1}{2}$
Calc lact.	grs	$7\frac{1}{2}$

many unpleasant symptoms and acting as a cholagogue and antipyretic, aspirin helps the action of quinine.

Sinton has pointed out that there exists some similarity between an attack of malaria and an anaphylactic shock, caused by the absorption of foreign protein from the body of the malarial parasite. Alkalies and magnesium sulphate given along with quinine treatment relieve the condition. He believes that the alkali has a catalytic effect on the action of quinine on the plasmodium and helps to lower the hydrogen-ion-concentration of the blood. The method of treatment is as follows: On the first day 3 grs. of calomel and 1 oz. of magnesium sulphate are given; on the following day 60 grs. of sodium bicarbonate and 40 grs. of sodium citrate dissolved in 1 oz. of water is given for three doses every two hours; followed after half an hour by 10 grs. of quinine sulphate, 20 grs. of citric acid and 60 grs. of magnesium sulphate in 1 oz. of water. By this method 1 to 3 drs. of quinine can be given within a week. Sinton claims that this method of treatment yields much better results than when quinine is given without an alkali.

The oral administration is the simplest and most practicable and should be the method of choice. An agreeable method of giving quinine in solution to patients with gastric irritation or to fastidious persons is in the form of effervescent mixtures.* The intramuscular method is rarely required unless there is vomiting and other contra-indications to oral use or when oral route is not attended with any success. In any case not more than two injections need be given. In fact Fletcher has shown that after intramuscular injection quinine is absorbed less rapidly than after oral administration; moreover, it does not maintain an effective concentration of quinine in the body for a longer period than when it is given orally. The intramuscular injections are given indiscriminately, and often in cases where quinine is not indicated. This method is painful and may be followed by severe necrosis. The danger, however, appears to have been exaggerated. The intravenous route should be used only in pernicious cases and when immediate action is essential, as for instance in cerebral malaria. The dihydrochloride in 10 gr. doses dissolved in 10 to 20 c.c. of physiological saline should be used, and the injection made very slowly so that it will reach the heart in low concentration; at least three minutes should be spent over the operation. Where the blood-pressure is low it is always wise to add 2 to 3 drops of 1 in 1000 adrenaline

*R

Quinin. hydrochlor. gr 7½
Acid. cit. gr 15
Syr. limon. ms 30
Aq. chlorof. ad oz 1

R

Sod bicarb gr 20
Sod cit gr 20
Aqua ad oz. ½

One dose of each to be mixed and taken during effervescence

solution to prevent further and possibly a fatal fall in the pressure.

In chronic malarial fever with relapses, anæmia and enlarged spleen quinine is best given in combination with iron and arsenic either in the form of a mixture or in pill form *

(2) *Enlargement of the spleen.*—With the cure of malaria the size of the spleen is reduced, but the efficacy of quinine is greatly augmented if it is given with iron †

(3) *Malignant form of malarial fever*—Many deaths occur from this type of fever from want of courage on the part of the physician to administer quinine in sufficiently large doses. From the beginning without any reference to temperature or local symptoms, with stimulants if necessary, quinine should be given. Although it is well recognised that malignant malaria reacts quickly to quinine, it has been found that certain strains of this parasite in special localities are resistant to it, which can be successfully cured by atebirin (see page 462). Cases of malignant tertian malaria associated with persistent vomiting or threatened coma, should be treated with intravenous quinine, a suitable dose being 0.6 grm. (10 gr.) dissolved in 10 to 20 c.c. of physiological saline.

In the so-called *malarial cachexias*, especially those of the *hæmorrhagic type*, quinine is of questionable value. Quinine base has *no hæmolytic action*. If the effect in "black water fever" is real it must be due either to (i) decomposition product of quinine, or (ii) aiding the formation of hæmolysin.

(4) *Intermittent or remittent neuralgias* of malarial or non-malarial origin, often yield to quinine.‡

As regards *prevention of infection*, there is no evidence that the use of quinine is of any effect. But the term "prophylaxis" in relation to malaria is frequently employed to mean the prevention of clinical symptoms following infection and for this purpose it undoubtedly has its uses. Quinine prophylaxis in this sense has proved of great benefit in the case of prisoners in jails and when given to troops serving in malarious countries, and it has been found that the systematic quininisation of school children greatly reduces

*R

Aisen trioxid	gr. 1/24
Quinn. sulph	gr. 2
Pulv. ipecac	gr. 1/6
Ferr sulph	gr. 1
Ext nuc vom. sicc	gr. 1/4
Pil ihei co	gr. 1 1/2

†R

Quinn sulph	grs. 2
Ferr sulph	grs 2 1/2
Pulv. ihei	grs 5
Pulv. ipecac	grs 1/6
Sod. bicarb	grs 2 1/2
In powder or cachet	

‡R

Quinn. hydrochlor.	gr 5
Amidopyrin	gr 2 1/2
Caffein cit	gr 2

the spleen rate. In the case of threatened epidemic of malaria the prophylactic use of quinine will save many lives whilst in any malarious community it will have good effect by reducing the number of human carriers of benign tertian malaria, though it has no effect on the gametocytes of malignant tertian (crescents). It is particularly necessary that the quinine should be administered to children, who form the principal reservoir of the disease. The most effective dose for prophylactic purposes is 10 grs. daily, but it is seldom possible to do this and it is more usual to give 10 to 15 grs. twice weekly. The drug is best given in solution, but it is frequently impossible to give it in this way on a large scale. If tablets are used, the form of the salt used should be the dihydrochloride, these should be fresh and their solubility tested before use.

As an *ecbolic* it is prescribed in uterine inertia during labour, if there is no obstruction. Ten grains followed by a similar dose after one or two hours often strengthen weak pains. It may be used in small doses in amenorrhœa to stimulate menstrual flow.

As a *nervine tonic* it has been used with great benefit in a host of nervous diseases, generally in combination with iron and strychnine, as Easton's syrup.

Quinine in pregnancy.—Much confusion appears to exist regarding the use of quinine in this condition because of its ecbolic effect. As has been pointed out, there is more danger of abortion in an untreated case of malaria than when properly treated with quinine. Quinine should therefore be given irrespective of pregnancy and the patient carefully watched. In any case the dose should not be more than 5 grs. at a time and this dose will rarely excite uterine contraction. In patients with a sensitive uterus, or if there be any history of previous abortion or miscarriage, it should be combined with or followed by either potassium bromide, or, according to the urgency of the case, with a preparation of opium. In case of doubt use atabrin.

Other diseases.—In combination with urethane quinine is largely used in the injection treatment of varicose veins. The method is to insert the needle of the syringe into the lowest segment of the vein after the part has been cleaned, and to inject slowly after a little blood being allowed to flow into the needle. Keep the needle for 30 seconds, then withdraw and seal the puncture with collodion and wool, or strap it. The solution used is quinine hydrochloride 4 grm., urethane 2 grm., water 30 ml (Injectio Quininae et Urethani, B.P.C.). The initial dose is $\frac{1}{2}$ c.c. increased to 2 to 3 c.c. Pregnancy, acute phlebitis, deep thrombosis, skin diseases, diseases of the heart with failing compensation and renal disease are contra-indications. It should not be given during menstruation.

Untoward effects.—Quinine sometimes gives rise to certain unpleasant symptoms, *viz.* ringing in the ears with impaired hearing and vertigo; irritation of the bladder with frequent urination, common in old persons; hæmoglobinuria; contraction of the uterus and abortion in pregnant women; vomiting; itching, sometimes erythematous, papular or urticarial rash (these often appear after small doses and are due to idiosyncrasy); rarely profound collapse.

Caution.—Quinine should be avoided, or given very cautiously, in acute or subacute diseases of the middle ear, gastro-enteritis, extreme anæmia, active cerebral congestion, skin eruptions, such as erythema, urticaria, etc., black water fever, and to persons particularly susceptible to its influence.

Prescribing hints.—The routine method of giving quinine is by the mouth and preferably in solution. Plain tablets are absorbed easily unless they are made with a menstruum which may interfere with their solubility in the stomach. Mineral acids (1 m. to each grain) and solution of ferric chloride dissolve the sulphate, but unless an excess of acid is used, it will leave a persistently bitter after-taste. To avoid this it may well be given in an effervescing form dissolved in citric acid (see page 454), or simply suspended in water. To diminish cinchonism the sulphate may be dissolved by the aid of dilute hydrobromic acid in the proportion of 2 ms. of the acid for each grain of quinine. Too large doses of hydrobromic acid, however, are apt to cause diarrhoea. The after-taste of quinine is soon removed or not perceived at all if the patient swallows a little water after taking the drug, and chews a few bits of betel-nut, myrobalan (*haritaki*), unripe guava, or any other substance containing tannin. For children relatively large doses are required, and they tolerate quinine better. Quinine ethylcarbonate and aristochin being tasteless should be preferred.

Quinine is incompatible with the usual alkaloidal precipitants. The sulphate is sparingly soluble in water and requires a dilute mineral acid for its solution. With vegetable astringents it forms an insoluble tannate of quinine. When diluted with water the ammoniated solution forms a precipitate. Precipitate also tends to form with a solution of arsenate, arsenite, phosphate, citrate, tartrate, benzoate, or salicylate, as the resulting compounds are very sparingly soluble in water. With salicylate of soda, quinine forms an ugly looking mass (salicylate of quinine) which requires an addition of some mucilage.

If there is much gastric irritability, intramuscular injection may be given first, followed by the bi-salt by mouth. The intravenous injection should be resorted to only in cases of extreme urgency. It should be the method of choice in cerebral malaria. The antiperiodic virtue of quinine is greatly enhanced if combined with aspirin, because of the

secretion of bile which has a great solvent action on quinine. In many obstinate malarial fevers, Warburg's tincture may be employed with great benefit, but it should be used with caution, as it causes copious perspiration, fall of temperature and weakness and slowing of the heart. Totaquina may be administered in the form of powder, cachet, pill or in solution with an acid.* As it contains all the cinchona alkaloids it is of great value in benign tertian infection, where it acts better than quinine, but owing to the presence of cinchonine and cinchonidine it is more liable to produce gastric irritation and headache.

The strictest asepsis must be maintained when giving a hypodermic injection of quinine. Several cases are on record where tetanus followed from want of proper knowledge, *viz.*—

- (1) Using distilled water as sterile water;
- (2) not perceiving that altitude lowers boiling point of water; and
- (3) that quinine itself in the powder form may contain these spores. Boiling should not be used, as quinine is altered to quinotoxine in an acid solution. Hence sterilisation under filtration is the proper method.

QUINIDINE SULPHATE

(Quinidin. Sulph.)

Quinidine Sulphate

Source.—The sulphate of an alkaloid, quinidine, obtained from the bark of various species of *Cinchona*.

Characters—Colourless, needle-like crystals; taste, very bitter. Darkens on exposure to light. *Soluble* in 90 parts of water and in 10 parts of alcohol (90 p.c.). An aqueous solution is neutral, or weakly alkaline to litmus.

B.P. Dose.—3 to 10 grs. or 0.2 to 0.6 gm.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Quinidine is also used in malaria specially in the treatment of benign tertian infection.

Heart.—It is largely used in the treatment of auricular fibrillation, specially when there is no cardiac enlargement or valvular disease. In about 50 p.c. of cases it restores the normal rhythm of the heart, but the best results are obtained in cases of recent origin and where the symptoms increase with the onset of fibrillation. It is sometimes useful in auricular flutter, the normal rhythm being restored

*R̄

Totaquin.	grs 7½
Acid. cit	grs. 10
Syr. limon.	ms 60
Aq. chlorof.	ad oz. 1

without the intermediate stage of fibrillation. In a majority of cases relapse takes place which requires further use of the drug, but this produces no further beneficial effect. It acts by depressing the cardiac muscle which is more marked in the auricle than in the ventricle so that by reducing the conductivity it lengthens the refractory period by 50 p.c. or more and stops the circus movement. It also reduces the frequency of auricular contraction by reducing the excitability of the auricular muscle and thus stops extrasystole, and inducing normal rhythm benefits tachycardia. Its action differs from digitalis where the effect is due to produc-

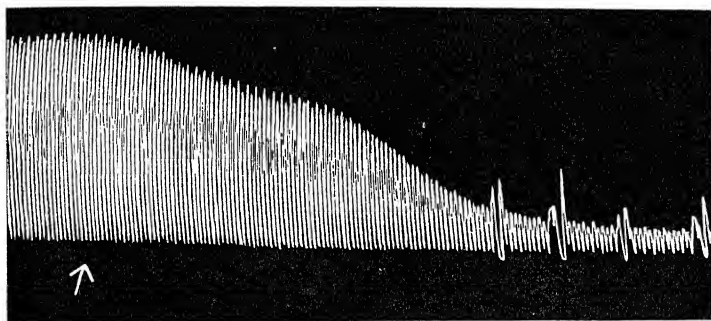


FIG. 24.—Record of the movements of Isolated Heart of a Rabbit perfused with Locke's solution.

At arrow a small dose of Quinidine was added to the perfused fluid. Note the depressant effect of quinidine on the heart. The contractions become weak and subsequently irregular.

tion of partial block in the auriculo-ventricular bundle thus protecting the ventricles from the innumerable impulses from the auricle.

It is rapidly eliminated, the maximum effect being attained in two hours which disappears after twenty-four hours.

The administration of quinidine is not entirely devoid of danger and sudden death during treatment has been recorded, and is possibly due to failure of the ventricular muscle. It frequently causes distressing symptoms, such as headache, nausea, vomiting, diarrhoea, abdominal pain, giddiness, faintness, buzzing in the ears, general distress, a sense of apprehension, palpitation, præcordial pain, excessive ventricular rate, orthopnoea, sweating, toxic erythema and urticaria. There may be marked idiosyncrasy when it becomes impossible to push the drug, although it is rather rare when the sensitiveness is so marked as to make treatment impossible. Slight degree of sensitiveness should not prevent a reasonable trial.

According to Hay cases unsuitable for quinidine are:—

1. Badly damaged hearts with old-standing valvular disease, and more particularly when there is failure of compensation with venous engorgement; here digitalis is the best drug to use.

2. In patients who suffered severely from angina pectoris, the onset of fibrillation is followed by the cessation of the anginal pain, and it is a question whether one should attempt to restore the normal rhythm

3. Where there is idiosyncrasy for the drug

4. Infective endocarditis.

5. Cases with a history of embolism

Cases suitable for quinidine:—

1. When the fibrillation is of recent origin, and when there is not much dilatation of the heart and no valvular disease.

2. Where the fibrillation is due to, or associated with, an acute infection.

3. When the onset of distress definitely dates from the inception of fibrillation, and it is clear that the abnormal rhythm is the disabling factor.

4. When the fibrillation is associated with exophthalmic goitre, specially where partial thyroidectomy has been performed and the fibrillation persists.

Prescribing hints—It is usually given in powders, cachets or in capsules in 6 gr. doses three times a day. But it is better to determine the patient's idiosyncrasy to the drug by giving an initial dose of 3 grs. The treatment should be continued for ten days and if the normal rhythm is not restored during the period, the chances are that quinidine will not prove successful. With each dose the pulse should be taken, and the use of the drug should be discontinued at least temporarily if the pulse is found to be regular. The total daily dose should not exceed 45 grs. Hay recommends that the daily dose should be given in ten equal doses, every two hours, as its action soon passes off.

ET YL Y CUP EINAE Y C LO I U

Optochin Hydrochloride. (Not official)

An artificial alkaloid closely related to quinine. A whitish amorphous powder with a bitter taste. *Cupreine*, is an alkaloid obtained from *Remyia* (*Cupiea* Bark)

Dose—1 to 4 grs or 0.06 to 0.25 grm

Uses.—Its actions are similar to quinine, but it has a specific bactericidal action on *pneumococcus*. In dilutions of 1 in 100,000 it prevents, and in 1 in 400,000 in serum it kills, the growth of these organisms. It has been successfully used in experimental pneumonia of mice, but has not proved a success in man owing to its untoward effect on the eye even when used in therapeutic doses. Effective doses are unsafe. It is however largely used in ophthalmic practice

either in the form of lotion (1 to 2 p.c.), or as ointment, in corneal ulcers (*ulcus corneæ serpens*), gonorrhœal conjunctivitis, scrofular ophthalmia and keratitis.

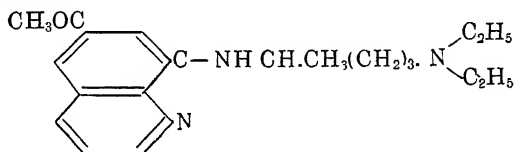
PLASM QUINE

$C_{19}H_{29}ON_3$ (Not official)

Syn.—Plasmochin

Source and characters.—A synthetic preparation of quinoline ring. It is *n*-diethylamino isopentyl-8-amino-6-methoxyl chinolin. A tasteless brilliant yellow granular powder. Soluble in alcohol and water up to 0.08 p.c. at 20°C.

Dose — $\frac{1}{8}$ gr. or 0.01 gm. in tablets



ACTION AND USES

This synthetic product has been introduced recently as a remedy for malaria, and has been found effective in benign tertian and quartan malaria, destroying all forms of *P. vivax* and *P. malariae*, in doses of 0.06 gm. (1 gr.) to 0.1 gm. ($1\frac{1}{2}$ gr.) daily. The therapeutic effects of curing primary attacks of these two types of malaria are about equal to that of quinine, but for curing malignant tertian fever its effect is not so good. Moreover, when used in the above mentioned doses the toxic symptoms often appear. Although it has no effect on the asexual (fever-producing) stages of the malignant tertian parasite, and the parasites multiply unchecked, it possesses the power of destroying the gametocytes of *P. falciparum* in the peripheral blood. This action makes this remedy of great value as a prophylactic, as it prevents the development of the *crescents* in the mosquito host; and for this purpose very small doses (0.02 gm. or $\frac{1}{2}$ gr.) twice a week are given.

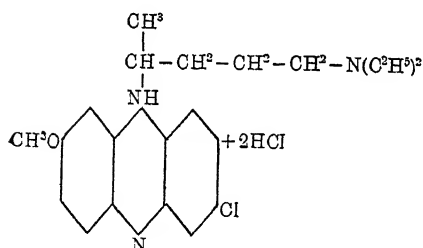
For routine treatment of acute attacks the dose should not exceed 0.03 gm. ($\frac{1}{2}$ gr.) daily and it has been a common practice to use it in combination with quinine or atabrin. But in these small doses it has little or no curative effect on the asexual (fever-producing) stages of the parasite, and its use cannot be justified in the acute stage of a primary attack. It was however thought that small doses given daily in the acute stage might prevent the development of the sexual forms of the parasite, which appear as a rule on the seventh day of the primary attack. But the onset of crescents in the peripheral blood is not prevented or retarded even by larger doses. Its use should therefore be deferred until the acute stage of the disease has been overcome by either quinine or atabrin. When given simultaneously with atabrin it may

produce gastro-intestinal and other nervous symptoms. Even doses of 0.02 grm. ($\frac{1}{50}$ gr) daily if prolonged for ten or more days may cause toxic symptoms. Quinine and plasmochin are less toxic and are useful in preventing relapses.

A mass treatment with small doses of plasmochin has been employed in many places as an *antimalarial measure*, but the success depends upon the extent to which the group is under control, and Schulemann has expressed the opinion that anti-mosquito measures will be necessary, for though the drug will render the gametocyte carrier incapable of infecting mosquitoes, it will be almost impossible to treat every carrier in a particular place. Combined with anti-larval measures it has given remarkable results in many tea states in Southern India, but this treatment alone will be hopeless in an uncontrolled civil population.

Toxic action.—The symptoms may arise with startling suddenness, but as a rule they are less abrupt. Epigastric pain, nausea, cyanosis, fatigue, profuse perspiration, and cardiac troubles accompanied by attacks of vertigo and fainting are often seen. If it is continued, cyanosis spreads, the temperature rises, and an attack resembling black-water fever develops accompanied by destruction of red-blood cells, hæmolytic jaundice and black urine containing methæmoglobin. Even in this stage recovery takes place if the drug is stopped and the patient properly treated with injections of glucose and adrenaline. As a rule the symptoms of poisoning appear in those whose liver is already damaged, but some patients are specially susceptible to it.

ATEBRIN (Not Official)



Syn—Elion

It is a dihydrochloride of an alkylamino-acridine derivative. In yellow powder with a bitter taste. Soluble in water forming like quinine fluorescence under ultra-violet radiation.

Dose—0.1 gsm ($1\frac{1}{2}$ grs) or one tablet, three times a day for five days.

ACTION AND USES

Atebrin is absorbed rapidly and is detected in the urine within 15 to 30 minutes after a single dose of 0.3 grm. Its greatest concentration occurs in the urine during the first 24 hours. It is an exceptionally powerful drug and destroys the asexual forms of all the types of malaria parasites. The crescents of the malignant tertian are however not affected at all. Its effect on human malaria resembles that of quinine, *i.e.* it destroys all forms of benign tertian and quartan parasites. Therefore in the treatment of these two varieties of malaria, the choice between them must be decided on

other considerations than those of immediate therapeutic efficacy for the clinical cure of a primary attack. Some cases of quartan are resistant to quinine while others are to atebryn. Therefore when one drug fails, the other should be tried. For treating primary attacks of malignant malaria the Malaria Commission of the League of Nations are of opinion that atebryn is much more effective than quinine, but it has no value on the crescents. Although neither of these complies with the requirements of a *therapia magna sterilisans*, the Malaria Commission believe that it is not wise for general routine use that one of them should be preferred to other. In cases with severe vomiting or other complications which prevent oral administration, atebryn can be given *intravenously* or *intramuscularly*. But the best plan is to give one or two intravenous injections of quinine, followed by oral use of atebryn.

The usual method of treatment is to give three tablets daily for five days with a saline purgative in the morning. Sometimes it is given with 0.01 grm. ($\frac{1}{8}$ gr.) of plasmochin in subtertian malaria to destroy the crescents, but as mentioned before this should be done after the primary attack has been checked, and the two remedies should not be given together.

A valuable property of the drug is to prevent relapses, and it is largely used in chronic relapsing cases. It is a drug of choice when there is idiosyncrasy to quinine and in cases of pregnancy. Although recommended in black-water fever it should be used with caution in view of several recorded cases of methæmoglobinuria.

It is excreted slowly and has been found in the urine even eight or nine days after the expiry of the seven-day course. A portion is accumulated in the cells of the liver and spleen. Its presence in the urine is detected by adding sulphuric acid and heating, when a characteristic yellow colour forms, best seen by looking down the test tube.

Atebrin Musonate is used for intramuscular or intravenous injection, and is supplied in dry ampoules containing the water-soluble salt—Atebrin dimethane sulphonate—which corresponds to 0.1 to 0.3 grm. of Atebrin hydrochloride. To be dissolved in 3 or 9 to 10 mls of sterile water before injection. For intravenous injection the single dose of 0.1 grm. should not be exceeded.

Toxic action—Toxicity though low is common when the dose is large. Gastro-intestinal symptoms, *e.g.* vomiting with excessive perspiration and severe pain in the abdomen are commonly observed. Yellow staining of the skin with enlarged and tender liver was observed by the writer. The yellow colouration is associated with defective functioning of the liver and kidneys. Methæmoglobinuria has also been reported. Fatty degeneration of the liver and kidneys in dogs and cats was recorded by DeMello. A few cases with mental symptoms, *viz.* delirium, hallucination, have been recorded.

SYNOPTIC REPRESENTATION OF THE ACTION OF QUININE, ATEBRIN
AND PLASMOQUINE IN DIFFERENT TYPES OF MALARIA

Action on	Quinine (Q)	Atebrin (A)	Plasmoquine (P)	Remarks
Trophozoites	Disappear, reappearing after a variable interval. M.T. effective in larger doses. Parasitocidal on G. of B.T. and Q.T. slightly so or nil on G. of M. T.	Action same as Q. but little rapid. Relapse occurs later. In M.T. effect same as Q. Action more or less as Q.	Very slight action on B.T. & Q.T. None on M.T. Effective in all stages and species specially so in crescents.	Differences in action may be attributed to differences to differences of strains, persons and recurrence of attack.
Gametocytes (G)				
Acute clinical attack	Definite action on B.T. Less so on M.T.	Marked in both, especially in certain types of M. T. but contrary result possible.	Of no advantage	
Frequency of relapse	Common in B.T.	Less common	Prevents relapses especially in combination with Q. $\frac{1}{2}$ gr. (split into 2 doses of $\frac{1}{4}$ gr. each) daily for 2 days in a week with Q.; $\frac{1}{4}$ gr. daily for 5 days after A.	
Dose and duration of treatment	B.T., Q.T. 15 grs. M.T. 20 to 30 grs. daily for 5 to 7 days.	$4\frac{1}{2}$ grs. (split into 3 doses) daily for 5 to 7 days.		
Toxic effects	Cinchonism. Ringing in the ears even deafness temporarily, contraction of visual field (even temporary blindness) headache; these are all central in origin.	Gastro-intestinal irritation, nausea, vomiting, epigastric pains, collapse with profuse perspiration. Hallucinations and delusions. Prostration, palpitation. Yellow discoloration of the skin and conjunctiva.	Gastro-intestinal irritation with collapse and subnormal temperature and sweats. Methæmoglobinuria. Headache and dizziness.	

Class B. Antisymphilitics

HYDRARGY UM

Mercury. (Hydrarg)

Syn.—Quicksilver.

Source.—A liquid metal obtained from native mercuric sulphide.

Characters.—A shining, silvery-white, heavy liquid, divisible into globules. Extremely mobile. *Soluble* in nitric acid, and in boiling sulphuric acid.

B.P. Dose— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 gm Intramuscularly — $\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 gm.

OFFICIAL PREPARATIONS

1. *Injectio Hydrargyri*. Syn.—*Mercurial Cream*.—1 gr. of Hg. in 10 ms B.P. Dose.—5 to 10 ms or 0.3 to 0.6 mil (intramuscular).

2. *Hydrargyrum cum Creta*. Syn.—*Grey Powder*.—33 p.c. mercury. A greyish-blue powder. B.P. Dose.—1 to 5 grs or 0.06 to 0.3 gm.

3. *Pilula Hydrargyri* Syn.—*Blue Pill*; *Mercury Pill*—33 p.c. mercury B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 gm.

4. *Unguentum Hydrargyri* Syn.—*Blue Ointment*.—30 p.c. mercury.

5. *Unguentum Hydrargyri Compositum*. Syn.—*Scott's Ointment* or *Dressing*; *Compound Mercury Ointment*.—Contains 12 p.c. mercury.

6. *Unguentum Hydrargyri Nitratis Forte*. Syn.—*Ung. Hydrargyri Nitratis*; *Citrine Ointment*—Contains 67 p.c. mercury.

7. *Unguentum Hydrargyri Nitratis Dilutum*. Syn.—*Diluted Mercuric Nitrate Ointment*.—20 p.c. of the strong ointment of mercuric nitrate.

NON-OFFICIAL PREPARATIONS

1. *Injectio Hydrargyri Fortis*, B.P.C. Syn.—*Oleum Cinerum*, *Grey Oil*—Mercury 40, wool fat 26, liquid paraffin 70 Dose—1 to 2 ms or 0.06 to 0.12 mil intramuscularly every eight days

2. *Massa Hydrargyri*, U.S.P. Syn.—*Blue Mass*, *Blue Pill*—Mercury 33, oleate of mercury 1, glycyrrhiza powder 10, althea powder 15, glycerin 9, honey 32 For 100 pills. Contains 32 to 34 p.c. of mercury Dose—3 grs or 0.2 gm

3. *Pilula Colchici et Hydrargyri Co* Syn.—*Brodie's Gout Pill*—Dry extract of colchicum, 0.39, mercury pill, 1.04, compound extract of colocynth, 1.04, extract of thubarb, 1.04, all in gms for 12 pills, syrup of liquid glucose, q s Dose—1 to 2 pills

4. *Pilula Digitalis Composita*, B.P.C. Syn.—*Guy's Pill*, *Niemeyer's Pill*—Powdered digitalis, squill in powder and mercury pill, each 1 gr. and syrup of liquid glucose, q s Dose—1 to 2 pills

5. *Pilula Hydrargyri cum Creta et Opio*, B.P.C. Syn.—*Hutchinson's Pill*—Grey powder, 12 gr, Dover's powder, 12 gr, compound powder of acacia, 1 gr, syrup of liquid glucose, q s for 12 pills Dose—1 pill

Y ARGYRI IO I U U U

(Hydrarg. Iod. Rubr)

Red Mercuric Iodide. HgI_2

Syn.—Biniodide of Mercury; Mercuric Iodide

Source and characters.—A scarlet-red powder, obtained by the interaction of aqueous solutions of mercuric chloride and potassium iodide. *Solubility*.—Almost insoluble in water, but freely in solution of potassium iodide.

B.P. Dose— $\frac{1}{2}$ to $\frac{1}{4}$ gr. or 0.002 to 0.004 gm.

OFFICIAL PREPARATION

1. *Liquor Arseni et Hydrargyri Iodidi*. Syn.—*Donovan's Solution*.—Contains 1 p.c. of each salt; or $\frac{1}{2}$ gr. of each salt in 15 ms. B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATIONS

1 **Hydrargyri Iodidum Flavum, USP**—*Yellow Mercurous Iodide*—A bright yellow, amorphous powder, contains not less than 99 p.c. of pure HgI . Becomes greenish on exposure to light. Insoluble in water, alcohol and ether. *Dose*— $\frac{1}{8}$ gr. or 0.01 gm.

2 **Hydrargyri Iodidum Viride** *Syn.—Green Iodide of Mercury, Protoiodide of Mercury*—In greenish yellow, odourless and tasteless powder. Insoluble in alcohol, ether and water. *Dose*— $\frac{1}{8}$ to 1 gr. or 0.01 to 0.06 gm.

3. **Unguentum Hydrargyri Iodidi Rubri, B.P. 1914**—Mercuric iodide 4 p.c. in benzoinated lard.

Y A GY U OLEATUM

(Hydrarg. Oleat.)

Oleated Mercury

Source and characters.—A light yellowish unctuous substance obtained by triturating yellow mercuric oxide 20 gms, liquid paraffin 5 gms. and oleic acid 75 gms. Heat to 50°C . Contains equivalent of 20 p.c. of mercuric oxide.

OFFICIAL PREPARATION

1. **Unguentum Hydrargyri Oleati**—25 p.c.

Y A GY I OXI UM FLAVUM

(Hydrarg. Oxid. Flav.)

Yellow Mercuric Oxide. HgO

Source and characters.—An orange-yellow, amorphous powder; obtained by the interaction of aqueous solution of mercuric chloride and sodium hydroxide. Insoluble in water. Contains not less than 99.3 p.c. of pure mercuric oxide.

Enters into.—Hydrargyrum oleatum, ung. hydrargyri oleati.

OFFICIAL PREPARATIONS

1. **Oculentum Hydrargyri Oxidi.**—1 p.c. yellow mercuric oxide.
2. **Oculentum Atropinæ cum Hydrargyri Oxido.**—Atropine 0.125 p.c.; yellow mercuric oxide 1 p.c.

Y A GY I PE C L RI U

(Hydrarg. Perchlor.)

Mercuric Chloride. HgCl_2

Syn.—Corrosive Sublimate; Perchloride of Mercury.

Source—Obtained by the direct combination of mercury and chlorine. Contains not less than 99.5 p.c. of HgCl_2 .

Characters—Heavy, colourless or white, rhombic crystalline masses, or a white crystalline powder. When heated, it fuses to a colourless liquid, which on further heat volatilises as a dense white cloud. *Soluble* in 18 parts of water, in 4 parts of alcohol (90 p.c.), in ether, and in glycerin.

Incompatibles.—Alkalies and their carbonates, potassium iodide, lime water, tartar emetic, silver nitrate, albumen, lead acetate, soaps, and vegetable astringents.

B.P. Dose.— $\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0.002 to 0.004 gm.

OFFICIAL PREPARATION

1. **Liquor Hydrargyri Perchloridi.**— $\frac{1}{8}$ gr. in 60 ms. or 0.1 per cent.
- B.P. Dose.**—30 to 60 ms. or 2 to 4 mils.

Y RARGY I SU CHLO IDUM

(Hydrarg. Subchlor.)

Mercurous Chloride. HgCl

Syn.—Calomel; Hydrargyri Chloridum Mite, U S P.; Subchloride of Mercury

Source.—A salt obtained as a sublimate when a mixture of mercurous sulphate and sodium chloride is heated.

Characters.—A dull white, heavy, nearly, tasteless powder. *Solubility.*—Insoluble in water, alcohol (90 p.c.), or ether. Volatilises when heated.

B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm. $\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. by intramuscular injection.

OFFICIAL PREPARATIONS

1. **Lotio Hydrargyri Nigra.** *Syn.*—*Black Wash.*—0.7 p.c. mercurous chloride

2. **Injectio Hydrargyri Subchloridi.** *Syn.*—*Calomel Injection.*—Contains 1 gr. calomel in 20 ms. B.P. Dose.—10 to 20 ms. or 0.6 to 1.2 mils, by intramuscular injection.

3. **Unguentum Hydrargyri Subchloridi.** *Syn.*—*Calomel Ointment.*—20 p.c. calomel.

NON-OFFICIAL PREPARATIONS

1. **Pilula Hydrargyri Subchloridi Co** B.P.C *Syn.*—*Plummer's Pill.*—Calomel 12 grs, sulphated antimony 12 grs, guaiacum resin 24 grs, gum acacia and tragacanth, each $\frac{3}{4}$ gr, syrup of glucose, q s. for 12 pills *Dose*—1 to 2 pills.

2. **Unguentum Hydrargyri Subchloridi Compositum**, B.P.C *Syn.*—*Calomel Cream, Prophylactic Ointment*—Mercurous chloride, 1 oz, mercuric oxycyanide, $1\frac{1}{4}$ gr, wool fat, 1 oz 175 grs, yellow soft paraffin, 1 oz, liquid paraffin, 262 $\frac{1}{2}$ grs

YDRARGY U A ONIATU

(Hydrarg. Ammon.)

Ammoniated Mercury. NH_2HgCl

Syn.—White Precipitate.

Source.—Obtained by the interaction of ammonia and perchloride of mercury. A white, odourless powder. Insoluble in water, alcohol (90 p.c.), and ether.

OFFICIAL PREPARATION

1. **Unguentum Hydrargyri Ammoniat.** *Syn.*—*White Precipitate Ointment.*—5 p.c. ammoniated mercury.

HY RARGY I OXYCYANI U

(Hydrarg. Oxycyanid.)

Mercuric Oxycyanide

Source.—Prepared by the interaction of mercuric oxide and excess of mercuric cyanide in the presence of water. Contains not less than 20 p.c. and not more than 22 p.c. of HgO , and not less than 77 p.c. and not more than 79 p.c. $\text{Hg}(\text{CN})_2$.

Characters.—A white crystalline powder. Almost completely soluble in 18 parts of water, solution alkaline to litmus.

B.P. Dose.— $\frac{1}{2}$ to $\frac{1}{2}$ gr. or 0.005 to 0.01 grm (intramuscular), $\frac{1}{2}$ gr. or 0.01 grm. (intravenous).

E SALYLU

Mersalyl. (Mersal.)

Syn.—"Salyrgan."

Source.—Is the sodium salt of salicyl-(γ -hydroxymercuri- β -methoxypropyl)-amide-O-acetic acid. Prepared by the action of mercuric acetate and methyl alcohol on salicylallylamide-O-acetic acid, and subsequent conversion to the sodium salt. Contains 2.5 to 2.8 p.c. of N, and 38.5 to 40.5 p.c. of Hg.

Characters.—A white powder; odourless; taste, bitter. Deliquescent. Soluble in about 1 part of water, and in about 3 parts of alcohol (95 p.c.)

OFFICIAL PREPARATION

1. **Injectio Mersalyli.**—Contains about 3 grs. of mersalyl, and about 1½ gr. of theophylline in 30 ms. B.P. Dose.—8 to 30 ms. or 0.5 to 2 mils.

ADDITIONAL NON-OFFICIAL PREPARATIONS OF MERCURY

1. **Hydrargyri Benzoas**—A white crystalline powder Dose— $\frac{1}{16}$ to $\frac{1}{10}$ gr. For hypodermic injection in solution which should be prepared fresh Hydrag Benzoas 1 grm, Sodium Chloride 0.75 grm, Water 100 grm. Dose—1 to 2 mil rising to 5 mil.

2. **Hydrargyri Succinimidum, U.S.P.**—A soluble preparation used for hypodermic injection Dose— $\frac{1}{4}$ gr. Solution generally used is Succinimide $\frac{1}{4}$ gr., Cocaine Nitrate $\frac{1}{8}$ gr., Aqua 12 ms. Dose.—6 to 12 ms. for an injection

3. **Hydrargyri Salicylas, U.S.P.**—A white powder slightly soluble in water. Powerful antiseptic and antisymphilitic. For *symphilitic sores*, as ointment or dusting powder. Dose, U.S.P.—1 gr. or 0.06 grm. twice a week as injection.

4. **Hydrargyri Tannas**—A green tasteless powder decomposed by weak alkalis setting free globules of mercury. Rapidly absorbed from the intestine without the disagreeable symptoms of mercurials, and producing best results in syphilis Dose—1 to 2 grs. or 0.06 to 0.12 grm. in pill

5. **Novasurol Syn—Merbaphen, U.S.P.**—A double salt of sodium mercuri-chlorophenyl-oxyacetate with diethylbarbituric acid. Contains 39 p.c. of Hg. Valuable in *portal cirrhosis, ascites*, and *cardiac edemas*, when it is more effective than digitalis or puuin derivatives. White crystalline odourless powder, soluble in water, with slightly alkaline reaction. A powerful *diuretic*. Contra-indicated in acute nephritis and enteritis.

Dose— $2\frac{1}{2}$ gr. or 0.15 grm. in 10 p.c. solution, intramuscularly or intravenously, once or twice a week

6. **Neptal—Hydroxymercuripropionamide of orthoacetyloxybenzoic acid**—Action similar to salyrgan when given by intramuscular injection. Diuresis begins within two hours of administration. In *nephritis* and *edema* of cardiac and renal origin, and also in *pleural effusion*. Non-toxic Dose—0.8 to 1.5 mil

7. **Metaphen—4-Nitro-5-hydroxymercuri-0-cresol.** Contains 59.68 p.c. mercury. Incompatible with acids and alkaloids. Does not precipitate proteins or act on instruments. Used for sterilisation of skin, instruments and hands. More potent than corrosive sublimate. Usual strength is 1 in 5000

8. **Mercurochrome "220" Syn—Dibromo-hydroxy mercury-fluorescein.**—In iridescent green scales. Soluble in water. Contains 25 to 28 p.c. of mercury. A non-irritating antiseptic, largely used in *genito-urinary practice* in 1 to 2.5 p.c. solution. Said to be valuable in refractory cases of *cystitis, pyelitis*, etc. Used intravenously acts as a *powerful urinary antiseptic* during excretion. A $\frac{1}{2}$ to 1 p.c. solution as injection in gonorrhoea. A 2 p.c. solution of acetone-alcohol-water mixture has been advocated for sterilisation of the skin before operation. Use has been suggested in *B. coli* infection, 1 p.c. solution in *conjunctivitis, ophthalmia neonatorum* and *blepharitis*. As an internal antiseptic it has been used in *puerperal sepsis, meningitis* and *septicæmia* but the results have been disappointing, the dose being 15 to 20 c.c. of 1 p.c. solution in freshly distilled

water. Dose—*Intravenously*, 0.003 to 0.005 grm per kilo of body weight in 0.5 per cent solution

PHARMACOLOGY

Externally—Metallic mercury and its salts are absorbed by the unbroken skin and may be administered either as an inunction or by fumigation. They enter easily through the hair and sebaceous follicles as an oxide or a chloride in combination with the fatty acids of the sebaceous glands. On the denuded or mucous surfaces they produce the following definite actions:—(1) All mercurials are **antiseptics** and **disinfectants**, more specially the corrosive sublimate which is one of the most effective of all mercurials, since it dissociates easily and gives the maximum concentration of mercuric ions which produce the antiseptic effect. The chloride being soluble in lipoids penetrates into bacteria more easily and is a stronger antiseptic than the sulphate, nitrate and acetate of mercury. In dilutions of 1 in 500,000 the chloride prevents the growth of, and in 1 in 25,000 kills, ordinary bacilli. The ammoniate, nitrate, oleate and oxide destroy animal parasites, and are valuable **parasitocides**. (2) Weak solutions of corrosive sublimate ($\frac{1}{4}$ to $\frac{1}{2}$ gr. in 1 oz), mercurous and many mercuric ointments are anti-phlogistic, astringent, stimulant and resolvent. (3) Stronger solutions, as the acid nitrate and the perchloride, cause inflammation and the concentrated ones sloughing.

The usefulness of mercurial salts as germicides is limited. They are precipitated by proteins, they are irritants and have an injurious effect on tissue, and are poisonous when absorbed. It is customary to add some sodium or ammonium chloride to prevent precipitation and to reduce their irritant effect. These form double salts which are less dissociated and therefore less active. Hydrochloric acid and tartaric acid are also used for the same object.

The bactericidal power of mercurials depends upon the concentration used, and whereas they act rapidly in high concentrations, they require longer time in dilute solutions. Thus while corrosive sublimate kills typhoid bacillus with a dilution of 1 in 100,000 in 24 hours, it takes 22 minutes with 1 in 20,000, and $2\frac{1}{2}$ minutes with 1 in 1000. Its action is probably due to adsorption, consequently sufficient time must be allowed to enable the drug to penetrate into the bacteria before they are killed.

Mercury arrests movements of the white blood-corpuscles and prevents suppuration. The ointments reduce swellings and promote absorption of subcutaneous effusions.

Internally **Gastro-intestinal tract.**—Mercurial salts affect the mouth, gums and salivary glands, causing **salivation** and **stomatitis**. This is not the result of direct local action but takes place during the process of excretion by

the salivary glands, for it occurs whether mercury is given by the mouth, subcutaneously or as inunction, and since the saliva contains the metal, it has a metallic taste. The salivation is due to parasympathetic stimulation (Meyer and Gottlieb), and is an important and earliest symptom of excessive therapeutic use and of chronic poisoning

Most of the preparations of mercury pass through the stomach unchanged and rarely cause any symptoms of irritation like nausea or vomiting, although taken in large doses, as in cases of acute poisoning, there is inflammation, congestion, hæmorrhage and necrosis. In the intestine they form some compound with albumin. But only a small portion of calomel enters into this combination, as quite a large portion of it can be recovered from the stool in an inorganic form. In the duodenum and upper part of the small intestine, insoluble mercury, such as grey powder, blue pill and calomel irritate the intestines to increased peristalsis beginning in the duodenum and extending through the whole length of the gut and diminish the absorption of fluid. As a result of this action the contents are hurried down so rapidly that the bile is not reabsorbed as happens normally, consequently the stools are dark green (calomel motions). X-ray examinations have shown that generally both the small and large intestines are stimulated. Mercurials are therefore **purgatives**. But the soluble preparations, or those salts which become soluble in the stomach, are too irritant to the stomach to be used as such. The stools are usually soft and there is no pain or straining. The purgative action is greatly helped by salines given a few hours later. If the dose is insufficient, or if it fails to produce purgation, or sometimes from idiosyncrasy, mercury may be absorbed producing constitutional symptoms, but is afterwards re-excreted into the bowels as sulphide

Mercurials are often credited with some disinfectant action in the intestine. They limit decomposition of food, and retard putrefactive changes in the duodenum and intestine, and check flatulence. The disinfectant action, if any, is very slight and possibly is the result of the purgative action which removes the decomposing fæcal mass. Large doses may favour bacterial growth by diminishing the intestinal resistance. They have little effect on unorganised ferments of digestion.

Liver.—Mercurials do not increase the amount of bile formed in the liver, although some bile appears in the stool. They aid excretion of bile already formed and are **indirect cholagogues**. The green calomel stools have been ascribed to the antiseptic properties of mercury checking the growth of bacteria in the gut, and so preventing the normal conversion of bile pigments into stercobilin. Since the green colour occurs in the absence of bile, some attribute it to the

presence of sulphide. After a brisk mercurial purgative there is improvement of portal circulation and the condition of the liver improves.

Blood and circulation—Mercury has very little direct effect on the heart and vessels, and the changes observed in the pulse in acute poisoning are really due to shock. In chronic poisoning they are the result of cachexia and malnutrition. Continued long in small doses, mercury not only increases the number of red cells, but increases their hæmoglobin. In this sense it may be considered as a tonic. In large doses it causes anæmia; but how far these effects are due to the improvement or impairment of digestion, or to the action on the blood itself, is not known.

Kidneys—Calomel, or sometimes blue pill, in 3 to 5 gr. doses, occasionally acts as a diuretic, specially in the presence of dropsy. But mersalyl and novasurol are more efficacious than other mercurial salts. These cause profuse diuresis even in normal individuals, and act better when a mild degree of acidosis is produced by the use of ammonium chloride. They act directly on the kidneys and do not increase glomerular filtration but act on the tubules and diminish reabsorption of fluids. Diuresis starts within 6 to 8 hours. When purging follows the use of mercurials less diuretic effect is observed. Since mercury is a protoplasmic poison and is concentrated in the kidney, large doses produce acute nephritis and necrosis of the epithelium of the tubules, congestion and acute inflammation of the glomerulus. These effects are more common with soluble preparations than with insoluble salts as they do not accumulate in sufficient concentration in the blood to produce them. Calomel, or blue pill is often used in combination with digitalis and squill in the form of Guy's pill. (See page 267).

Absorption and elimination.—Mercurials are freely absorbed from all surfaces, and after absorption they disappear rapidly from the blood and are deposited in the different organs, chiefly the kidneys, the intestinal walls, and the liver, probably in the form of albuminate. From these depots mercury may be mobilised for several months even after the stoppage of the drug. It begins to be excreted within a few hours of its administration, and may last for several days after a single dose. It is excreted chiefly by the kidneys, and also by the cæcum and colon. The organic compounds are eliminated mainly by the kidneys, while the inorganic compounds by the fæces. The elimination is very slow. Therapeutic administration does not as a rule produce an excretion of more than 10 mg. of mercury daily by the kidneys. Whenever the daily excretion is above this, the kidneys suffer injury. The concentration of mercury in the kidneys is higher than in the blood. It is also excreted by the saliva, sweat, milk, gastric juice and bile, but a large

portion is reabsorbed from the intestine which makes the quantity excreted in the fæces variable. It has been traced to the fœtus through the placental circulation.

Specific action—Mercury is specific in syphilis, specially in the primary and secondary stages. This is due to its action as a parasiticide for *Spirochæta* (*Treponema*) *pallida*, for mercury in 1 in 20,000 destroys spirochæta in test tubes. It is not possible to estimate the exact amount present in the tissues, but probably it acts in very great dilutions, and is a valuable *chemotherapeutic agent* in the treatment of syphilis. It has no lethal effect on other protozoal infections like malaria or sleeping sickness.

Toleration.—Age, sex, and idiosyncrasy greatly modify the action of mercurials. Children as a rule bear mercury better than adults, and males better than females. Patients suffering from granular kidneys, scrofula, scurvy and malarial cachexia are specially susceptible to this drug. Some are very susceptible to it so that a very small dose may cause salivation. Pregnancy is no bar to the administration of mercury.

Acute toxic action.—This is generally due to accidental or suicidal swallowing of tablets or solutions of perchloride, and has been known to follow the retention of strong solution used as uterine or vaginal douches. If a strong solution is taken there is local corrosion of the mouth, œsophagus and stomach with abdominal pain, vomiting, purging and the passage of serous or bloody stools; salivation, metallic taste, burning and an ashy discoloration of the mouth and pharynx. Congestion of the stomach and small hæmorrhages, hyperæmia, redness and swelling of the mucous membrane, developing into necrotic surfaces and ulcers along the folds are observed chiefly in the cæcum and colon, the small intestine almost entirely escaping. Mercurial stomatitis develops within 24 hours. The urine becomes albuminous and bloody with casts. Very soon anuria follows with delirium, coma, collapse and death. In a recent case hæmatemesis and melaena with anuria were prominent symptoms before death. Very little effect is observed on the nervous system and intellect remains clear to the end.

Treatment—White of several eggs should be given immediately so as to form a non-corrosive albuminate, followed by immediate lavage of the stomach. After this a pint of milk may be introduced into the stomach which may be removed by lavage if vomiting continues. If the stomach permits, early feeds of milk alternating with potassium bitartrate mixture are useful. Sodium hypophosphite 1 grm; water 10 c.c. and hydrogen peroxide 5 c.c. per 0.1 gm. of mercuric chloride is more effective (Sollmann). Sodium thiosulphate intravenously has proved of no value. Irrigation of the colon morning and evening is also advisable. This is continued until no mercury is found in the urine on two successive days. The use of alkalis gives the best protection against development of tubal nephritis. If the anuria is not overcome, copious fluid injection may lead to pulmonary oedema.

Chronic toxic action, Hydrargyrisms or Mercurialism.—This is now rare, but occurs occasionally either as the result of accident or malpraxis, and among workers in mercury. The first indications of mercurial poisoning are fætor of the breath and soreness of the gums (the medicinal administration of mercury should not go further) soon followed by a disagreeable metallic taste; swollen, red, spongy gums,

bleeding on the least touch; and increased salivary discharge. The appetite disappears, there is a feeling of weight and discomfort in the stomach, with nausea, colicky pain and diarrhoea. Skin eruption often appears even when given by the mouth, though more common when used as inunction. These symptoms increase, the tongue becomes furred and swells, the tonsils and pharyngeal glands enlarge, there is swelling and tenderness of the parotid and submaxillary glands, the teeth get loosened, the gums recede and become ulcerated, the saliva gets thick and viscid, and pours out of the month, fever and depression set in. If the dose is large and long continued these symptoms are aggravated, and end in the falling out of the teeth, ulceration and abscess of the month, necrosis of the jaw-bones, great prostration, anaemia, emaciation, repeated hæmorrhage, and death.

Protracted exposure to a moderate degree of mercurial vapour produces a different train of symptoms generally known as **mercurial paralysis**. Besides the cachectic symptoms there are muscular tremors, first beginning at the face, then invading the arms and the legs, extreme weakness of the affected muscles; mental weakness, and functional disturbance of special senses. These tremors increase by attempts at voluntary movement, *i.e.* they are "intention tremors." A condition known as **mercurial erethismus**, is characterised by hyper-irritability, restlessness, timidity or shyness, muscular weakness, or sleeplessness. Delirium with transitory hallucination may appear.

Metallic mercury vaporises even at the ordinary temperature and may produce poisonous effects even though the evaporating surface be small if the emanations from it continue for any length of time.

Several cases are on record in which mercurial cachexia has resulted from vaporisation of the mercury with which the backs of mirrors are coated.

THERAPEUTICS

The therapeutic uses of mercury and its salts are five-fold: *externally*, they are (1) antiseptic, (2) antiparasitic; and *internally*, (3) antisymphilitic, (4) cathartic, and (5) diuretic.

Externally.—As an **antiseptic**, cyanide and perchloride of mercury are used, but the solution of the latter is largely employed for disinfecting purposes, as well as in **surgical and obstetric practice**. A solution of oxycyanide (1 in 5,000 to 1 in 10,000) is useful for washing out the bladder and urethra in gonorrhœa, while a lotion of 1 in 5,000 is used in ophthalmic work. As it does not attack metals the lotion can be used for instruments (1 in 200). A lotion of perchloride (1 in 1000) is used for washing infected rooms, furniture, articles, linen, the surgeon's and gynæcologist's hands, the parts to be operated upon, and for moistening dressing, towels, wool, etc. A lotion (1 in 10,000) may be ordinarily used for washing wounds and ulcers, but the former strength can be advantageously employed if they are foul or of syphilitic origin. A solution of 1 in 5000 is ordinarily used for irrigation of the bladder, vagina and uterus, but its strength requires to be diminished to 1 in 10,000 if used continuously for any length of time. Biniodide spirit lotion* is a valuable antiseptic for the skin and hand.

*R̄

Hydriag. iod	grm. 1
Pot. iod.	grm. 1
Alcoh. (70 %)	mil. 1000

The following are the disadvantages of perchloride of mercury as a disinfectant :—

- (1) It is very poisonous to man.
- (2) It corrodes metals.
- (3) It combines with albumin—forming an albuminate, on which account it is not good for the disinfection of fæces, unless an acid is also present.

As a parasiticide—Citrine, oleate and white precipitate ointments and perchloride lotion (1 to 2 grs. in 1 oz. of water) are employed to destroy the fungus of tinea, such as of ring-worm, mentagra, and favus ; and animal parasites, such as the various kinds of lice and their nits, and the *Acarus scabei*. The red oxide or citrine ointment is very effective in tinea ciliaris. The oleate is a useful application in pityriasis versicolor.

As a remedy for pruritus.—Blue ointment, calomel ointment (60 grs. to 1 oz.), and black wash relieve the distressing itching of many skin diseases, such as urticaria, prurigo, pruritus ani, psoriasis, lichen, pityriasis of the scalp and eczema. If applied with care and not to a large area, there is very little danger of salivation.

As a stimulant and promoter of absorption—The liniment and the various ointments, such as oleate, red precipitate, Scott's and red iodide are used for dispersing glandular enlargement, as buboes ; and for promoting the absorption of inflammatory products, as in chronic joint disease, chronic peritonitis and periostitis. Red iodide of mercury ointment is a good application for **goitre**, especially if the patient be made to sit in the sun or before a fire immediately after the application has been made.

As an antiphlogistic.—Diluted citrine ointment if applied over whitlows and boils and then covered with plaster rapidly causes them to abort. Mercurial ointment is useful in onychia and paronychia. A ten minutes' application followed by a poultice every hour cuts short the inflammation.

As a specific—Mercurial ointments and black wash are always prescribed for dressing over chancres and other syphilitic sores. Black wash is an unirritating application, when the sores are kept wet with a bit of lint soaked in it. Nothing is so good as to wash all suspicious sores with a perchloride lotion (1 in 500). A cyanide of mercury lotion (5 to 15 grs. in water 1 oz.) is a good local application to syphilitic sores. Besides their use in syphilitic sores, they are of great service in all varieties of skin diseases, originating from syphilis. It should be borne in mind that in all syphilitic sores the local application must be combined with internal administration of anti-syphilitic remedies like bismuth, mercury or arsenic.

Eye—Mercury is used in certain diseases of the eye, e.g. in conjunctivitis, blepharitis and keratitis. For this purpose oculentum hydrarg. oxid. is generally used. Finely powdered

calomel is also applied locally in syphilitic and other affections of the eye (phlyctenular ophthalmia). When applied in this way potassium iodide must not be simultaneously administered internally, otherwise it will appear in the lachrymal secretion and then, mixing with the calomel, will produce an iodide of mercury, and violent inflammation of the eye will be the result.

Internally. **Gastro-intestinal tract**—Local syphilitic sores in the mouth soon heal under the use of the perchloride mouth-wash.* **Vomiting** in infants whether occurring immediately after feeding or at other times is stopped by grey powder in $\frac{1}{2}$ gr. or $\frac{1}{8}$ gr. given every two or three hours. **Infantile diarrhoea** whether acute, subacute or chronic, with clay-coloured, offensive, or dark green, or slimy, or curdy, stools, soon yields to small doses of calomel or grey powder. In **infantile cholera**, the vomiting and purging are soon arrested by an hourly dose of grey powder ($\frac{1}{8}$ gr.), while fractional doses of calomel ($\frac{1}{2}$ gr. to $\frac{1}{8}$) have been found useful in the early treatment of cholera when given every hour till the colour of the stool alters. Cases of obstinate **hiccough** have been checked by small doses of calomel. Blue pill or calomel is given as a **purgative**, but it should not be prescribed to habitual opium-eaters, or to a patient under opium treatment, for fear of absorption and constitutional symptoms. In every case, it is a good plan to follow the mercurial by a saline aperient. Calomel or grey powder in small doses or as a purgative clears the thickly coated creamy tongue of many acute diseases.

In biliousness or hepatic derangement due perhaps to free living, a dose of blue pill or calomel at night, followed by a dose of compound senna mixture, or Seidlitz powder or compound liquorice powder next morning, produces excellent results.

Inflammatory diseases.—Few now prescribe mercury in acute inflammatory diseases, except in iritis, but there are many who yet use it in meningitis and inflammation of the serous membranes in conjunction with iodides.

Dropsy and ascites.—Calomel given several times a day acts as a diuretic in **cardiac dropsy**. Its efficacy is greatly increased if combined with digitalis and squill, as in Guy's pill (see page 267). It benefits, though temporarily, **ascites** due to **cirrhosis** of the liver. It should not be given in renal dropsy. Mersalyl and novasurol are now extensively used as diuretics in ascites and in cardiac and other dropsies. The injections are given intravenously or intramuscularly according to the urgency of the case. An initial

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Hydrarg perchlor	gr	4
Acid. hydrochlor dil	ms	10
Aqua	ad oz	10

dose of 0.5 mil is given to test the tolerance of the patient, and subsequently increased to 2 mils and is given once or twice a week. The effect lasts for eight to ten hours. It acts better when partial acidosis is produced by the administration of ammonium chloride for a few days prior to the injection. Mersalyl is less toxic than novasurol. Since mercury has a special toxic effect on the kidney, these drugs are best used in cardiac dropsies and should not be used in acute and advanced nephritis.

Syphilis.—The most important use of mercury is in the treatment of syphilis, and as has been pointed out this is due to its specific poisonous effect on the *Treponema pallida*, the organism of syphilis. Brilliant though the results are with organic arsenic compounds in the treatment of this disease, the fact remains that we cannot do without mercury. For it has been found that to get the best results it is necessary to use both the drugs, or bismuth in place of mercury. Whereas the concentration necessary to sterilise the tissue with arsenic is obtained quickly, it requires several weeks to obtain the same result with mercury. It is therefore necessary that as soon as the case is diagnosed and before the parasites migrate into more inaccessible parts of the body, one of the arsenic preparations should be used at an interval of one or two weeks, and the mercurial treatment should be adopted immediately afterwards. Because of lower toxicity bismuth is preferred by many to mercury.

It is true that in these modern days injections of various salts of mercury have somewhat replaced oral method of administration, as in this absorption is uncertain and there is a great liability to gastro-intestinal disturbance. But if a patient cannot be kept under the close supervision which the treatment by injection or inunction necessitates, then oral administration is of value. The treatment should be started as soon as the disease is diagnosed, and it is now recognised that the chances of success are greater the earlier the treatment is commenced. In tertiary syphilis mercury is used with iodides as the latter drug helps destruction of the gummatous tissues thus setting free the spirochaetes which are destroyed by the mercury.

By whatever method it is administered mercury tends to produce cumulative effects, therefore in the treatment of syphilis there must be periods of rest when the patient should not get any mercury. It is customary to stop treatment for a month after a period of four to six weeks. During this period the mercury stored in the tissues is gradually liberated and excreted.

Mercury is also valuable as a *prophylactic*, for this purpose calomel 33 p.c. with lanoline; or oxycyanide of mercury 0.66 grm., glycerin 50 c.c. and water to 500 c.c., heated in a water bath for 1 hour, may be applied as inunction into

the part exposed To be effective the application should be made within 4 to 5 hours after exposure. But its thorough application by women is impossible

For the treatment of syphilis mercury may be administered by the following methods:—

1 *By the mouth.*—This is by far the most convenient route, but it is rather difficult to administer sufficient mercury on account of its effect on the digestive tract and purgation which causes the absorption to be irregular. The preparations used by this route are innumerable. Blue pill, grey power, and calomel are generally used. Grey powder is the most widely used preparation, and since these insoluble compounds are liable to cause diarrhoea and looseness of the bowels, it is customary to combine it with opium in the form of Dover's powder, or to give one dose of this combination at bedtime. Protoiodide and sublimate are probably the most reliable remedies given internally. Dupuytren's pills are an example of the use of perchloride of mercury, each pill contains hydrarg. perchlor. $\frac{1}{8}$ gr., ext. opii $\frac{1}{2}$ gr., ext. guaiaci $\frac{3}{4}$ gr. The dose may be gradually raised avoiding salivation and always remembering variation in toleration. The mouth must be kept clean during the treatment. It is better to use the protoiodide in the early secondary and keep the sublimate for the late secondary and tertiary stages. With the sublimate gastric intolerance is frequent but salivation is not marked, with the protoiodide gastric intolerance is infrequent but stomatitis is more common

2. *Inunction.*—By rubbing blue ointment, liniment or oleate of mercury into the skin mercury can be rapidly introduced into the blood. The inner surface of the thigh or the axilla is a suitable spot for inunction. This method is specially useful for the treatment of young children; 20 to 60 grs. of blue ointment may be rubbed in nightly or every other night. The site of rubbing should be varied for fear of local irritation. The German ointment (1 of Hg. in 3) is no doubt superior to the B.P. preparation. The advantage of this method is that digestion is not disturbed, but it is dirty and disagreeable and special skill is required to avoid cutaneous irritation. By this method sufficient mercury can be introduced to produce saturation of the system in about two weeks.

3. *Injection.*—This may be *intravenous* or *intramuscular*. Where a very quick effect is desired the intravenous injection of 1 c.c. of 1 p.c. solution of the perchloride every other day has been suggested, but these tend to produce fibrosis which precludes the use of the vein for future injection, besides the risk of embolism and production of toxic symptoms. Only one-third of the maximum dose tolerated intramuscularly can be given intravenously without producing toxic effects, therefore the dose is less, but since mercury is excreted more

rapidly when given by this route these injections require to be repeated more frequently. Oxycyanide is more suitable for intravenous use in doses of $\frac{1}{8}$ gr. dissolved in 5 mls of sterile saline solution. But there is no evidence that a sufficient concentration of mercury can be produced in the blood by this route. As regards intramuscular injection the preparations may be *soluble* or *insoluble*. The advantages of the soluble preparations are that being more speedily absorbed their effect is more rapid and the exact quantity absorbed is known. The disadvantage is that rapid absorption means frequent injections either daily or on alternate days. The advantage of the insoluble preparation is that a large dose of mercury is put in, which usually suffices for a week, and that from these "depots" the mercury continues to be absorbed for some weeks. On the other hand the disadvantages are—accuracy of dosage is impossible, toxic symptoms may continue long after suspending treatment by absorption from the above mentioned "depots". The injection is made deep into the gluteal and lumbar muscles.

Amongst the soluble salts thus injected are the perchloride $\frac{1}{8}$ gr dissolved in 17 ms. of distilled water, to which a little sodium chloride $\frac{1}{8}$ gr. is added; or the mercury biniodide, or the oxycyanide in strengths of $\frac{1}{8}$ gr. The most powerful and undoubtedly the most effective of the insoluble salts is calomel although mercurial cream is also used. These possess the following advantages, *v z.*—

- (1) They are painless.
- (2) They are absorbed slowly and slowly excreted.
- (3) They are less likely to produce stomatitis and gastrointestinal irritation.
- (4) The therapeutic effects are more lasting.

Intraspinal injection of mercurialised serum has been advocated for the treatment of cerebrospinal syphilis. It is prepared by adding 1 c.c. of 0.13 per cent. mercuric chloride to 12 c.c. of normal human or horse serum, heating to 56°C. for one-half hour a clear solution is formed. This dose is injected by gravity at body temperature. The cerebrospinal fluid is first withdrawn till its pressure is 30 mm.

Caution—Unless appetite and digestion are good mercury should not be given by the mouth. Weak, anæmic and scrofulous subjects, and those suffering from kidney disease cannot bear mercurials. For fear of absorption it should not be employed over a large area. Concentrated solutions should not be used as injections into the vagina and uterus.

Prescribing hints.—As a purgative mercury is usually prescribed in the form of either calomel or blue pill. They may with advantage be used at bed time to be followed by a saline, either black draught, Epsom salts, Glauber's salt, or Seidlitz powder. Grey powder in fractional doses is a valuable remedy for children's dyspepsia. For the treatment

of syphilis mercury is generally given by the mouth either in solution or in the form of a pill and considerable quantity can be absorbed from insoluble compounds when given by the mouth. Grey powder is generally used in 1 gr. doses. To prevent looseness of the bowels it may usefully be combined with the same quantity of Dover's powder. This combination may be given in the form of pills, powder, or tablets. The administration of mercury should be stopped, or the dose reduced as soon as the patient begins to complain of soreness of the gums. Inunction is best suited for children, and hot baths aid absorption and elimination of mercury. The oxycyanide should not be used with potassium iodide. When mercury is not tolerated by the mouth the best method is the injection, and the official injections may be used for the purpose. Being insoluble they are less painful, and as the absorption is slow the injections are given less frequently, once or twice a week. As a diuretic mercury is given in the form of Guy's pill, or as injections of mersalyl or novasurol.

For external use the oleate is a very useful preparation and is non-irritant. The white precipitate ointment is a valuable antiparasitic and may be used diluted with equal parts of boric ointment. The student should remember that liquor hydrargyri perchlor. is incompatible with alkalies and when combined with carbonate of ammonia it forms an insoluble precipitate of ammoniated mercury, which is less poisonous and can be dispensed suspended with mucilage and a "shake the bottle" label used. With potassium iodide it forms potassium mercuric iodide. If however the carbonate of ammonia be added after this combination no precipitate of ammoniated mercury is formed. With tannic acid or substances containing it, salts of mercury form insoluble tannates.

℥ BISMUTHI CARBONAS

Bismuth Carbonate. (Bism. Carb.)

Syn.—Bismuth Oxycarbonate; Bismuth Subcarbonate.

Source.—Obtained by the interaction of bismuth nitrate and a soluble carbonate.

Characters.—A white or creamy-white powder; odourless and tasteless. *Insoluble* in water, completely soluble with effervescence in nitric and hydrochloric acids.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

OFFICIAL PREPARATION

1. Trochiscus Bismuthi Compositus.—2½ gr. in each.

BISMUTHI SALICYLAS

Bismuth Salicylate. (Bism. Salicyl.)

Syn.—Bismuth Subsaliolate.

Source.—Obtained by the interaction of solutions of bismuth nitrate and sodium salicylate.

Characters.—A white or nearly white, amorphous powder; odourless and tasteless. *Insoluble* in water.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm. By intramuscular injection :—1 to 2 grs. or 0.06 to 0.12 grm.

OFFICIAL PREPARATION

1. *Injectio Bismuthi Salicylatis.*—Contains 2 grs. of bismuth salicylate in 20 ms. **B.P. Dose**—10 to 20 ms. or 0.6 to 1.2 mils, intramuscularly.

ISMUT U P AECIPITATUM

(Bism. Præcip.)

Precipitated Bismuth

Source.—Obtained by the reduction of a solution of bismuth trichloride in hydrochloric acid by means of hypophosphorous acid. Contains not less than 98.5 p.c. of metallic bismuth.

Characters.—A dull grey powder. Easily diffusible in water. *Insoluble* in water.

B.P. Dose.—1½ to 3 grs. or 0.1 to 0.2 grm. intramuscularly.

OFFICIAL PREPARATION

1. *Injectio Bismuthi*—Contains 3 grs. in 15 ms. **B.P. Dose**—8 to 15 ms. or 0.5 to 1 mil, intramuscularly. This is known under the proprietary name of *Bismostab*.

ISMUT I ET SO II TART AS

(Bism. et Sod. Tart.)

Sodium Bismuthyl Tartrate

Syn.—Bismuth Sodium Tartrate.

Source.—May be obtained by the interaction of bismuth hydroxide and sodium acid tartrate. Contains 35 to 42 p.c. of Bi.

Characters.—A white powder, or slightly yellow scales. Soluble in less than 1 part of water.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm. intramuscularly.

ISMUT I XYCHLO I U

(Bism. Oxychlor.)

Bismuth Oxychloride

Syn.—Bismuth Subchloride.

Source.—A basic salt of varying composition, obtained by the interaction of solutions of bismuth nitrate and sodium chloride or hydrochloric acid. Contains 79 to 81 p.c. of Bi, and not less than 12.5 p.c. of Cl.

Characters.—A white or nearly white, amorphous or finely crystalline powder; odourless; tasteless. Stable in air. Insoluble in water, soluble in dilute hydrochloric acid.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm. By intramuscular injection :—1½ to 3 grs. or 0.1 to 0.2 grm.

OFFICIAL PREPARATION

1. *Injectio Bismuthi Oxychloridi.*—Contains 3 grs. of bismuth oxychloride in 30 ms. **B.P. Dose.**—15 to 30 ms. or 1 to 2 mils, intramuscularly.

NON-OFFICIAL PREPARATIONS

1. **Pasta Bismuthi et Iodoformi** *Syn*—B I P P—Mix bismuth subnitrate 1, iodoform 2, and stir in liquid paraffin 1 or *q s*
2. **Insufflatio Bismuthi et Morphina** *Syn*—*Ferre's Snuff*—Bism Subnitrate 180, Morph Hydrochlor 1, Powdered Gum Acacia 60. Mix Useful in *coryza*. A pinch each time till the nostrils are cleared
3. **Liquor Bismuthi et Ammonii Citratis, B P C**—Bismuth subnitrate, 70; citric acid, 52; dilute solution of ammonia, *q. s*, distilled water, *q s* 1000 *Dose*.— $\frac{1}{2}$ to 1 dr or 2 to 4 mls

ADDITIONAL DERIVATIVES OF BISMUTH

1. **Neo-Trepol**—Contains 10 p c of bismuth Is a suspension of finely divided precipitated metallic bismuth in isotonic serum Used intramuscularly and the injections are painless Useful in tertiary stages and in old cases with no apparent lesions but with a positive Wassermann reaction *Dose*—15 to 2 c.c every 3 or 4 days
2. **Bismogenol**—Suspension of bismuth salicylate in olive oil, containing .005 to 0.06 gm of bismuth per c c. Complete course 15 to 20 injections of 1 c c. given every 3rd day.
3. **Bismuth Arsphenamine Sulphonate.** *Syn*—*Bismarsen*—A yellow soluble, compound Arsenic 13 p c and bismuth 24 p c Valuable in early syphilis in 0.1 to 0.2 gm *intramuscularly* *Dose*—0.2 gm in 1 c.c. sterile water to which 2 ms of 2 p c solution of butyn has been added Two injections weekly.
4. **Quinine Bismuth Iodide** *Syn*—*Quinby*—Contains 23 p c of bismuth, 57 p c iodine, and 18 p c quinine. *Dose*—3 c c of an oily suspension
5. **Bismuth Beta-naphtholate** *Syn*—*Orphol*—Less irritating than naphthol A gastro-intestinal antiseptic and astringent *Dose*.—5 to 15 grs or 0.3 to 1 gm.
6. **Bismuth Oxyiodogallate** *Syn*—*Arrol*.—A greyish-green powder used as a substitute for iodoform, and injected as an emulsion with glycerin (10 p c) in *gonorrhoea*
7. **Bismuth Subgallate, U S P** *Syn*.—*Dermatol*—A yellow, odourless, non-irritating and non-poisonous powder, superior to iodoform as a dressing. It may be applied as a paste, powder, colloidion or ointment Found invaluable in *tubercular diarrhoea* It has been used also in *gastric ulcer* and *cancer*. *Dose*, U.S.P.—15 grs or 1 gm
8. **Bismuthi Subnitras**—A heavy, white inodorous powder with slightly acid reaction. Insoluble in water. *Dose*—5 to 20 grs or 0.3 to 1.2 gm
9. **Bismuth Tannate.**—A yellow powder, insoluble in water. Useful in *diarrhoea* and *dysentery*. *Dose*—5 to 30 grs or 0.3 to 3 gm
10. **Bismuthi Tribromophenae** *Syn*—*Xeroform*—A greenish-yellow powder. Powerful intestinal antiseptic, recommended in *cholera* Used also as a dusting powder in place of iodoform *Dose*—5 to 15 grs or 0.3 to 1 gm.

PHARMACOLOGY

Externally.—Bismuth salts have no action on the unbroken skin, but applied to wounds they dry the secretion and form a protective covering and help healing. The action is purely mechanical On the denuded surface they act as sedative, mild astringent and antiseptic.

Internally. **Gastro-intestinal tract.**—Bismuth salts blacken the tongue, have no taste and produce a feeling of roughness in the mouth. In large doses they act as direct sedative to the mucous membrane of the stomach and intestine. They act physically by shielding the nerve-terminations from the irritating secretions by forming an adhesive coating on the wall of the stomach and intestines, and so protect them from the irritation of food and secretions. As a

consequence of this sedative effect, they act as antiemetics and mild astringents. They also control fermentation, especially the salicylate, naphtholate, etc., and are therefore intestinal antiseptics. Bismuth subnitrate splits up into bismuth oxide and nitric acid in water, liberating nitrous fumes which tend to contribute toward the antiseptic property of the drug. It passes out with the faeces as a sulphide, colouring them leaden black.

Absorption and elimination.—Bismuth salts are not absorbed from the gut and even soluble preparations become insoluble powders and pass through the stomach and intestine unabsorbed as oxychloride in the stomach and as sulphide in the intestine. Very large doses have been given by the mouth for X-ray examination without eliciting any toxic symptoms. The rate of absorption when given intramuscularly depends upon the site of injection and on the nature of the preparation used. The exact manner in which it is absorbed is not known, although it is possible that the phagocytic cells may play some important part in this process. The rate of absorption is slow and varies with the dose, and the number and frequency of injection. The solubility of the preparation used is an important factor in the process of absorption. Insoluble compounds slowly become soluble by the interaction with the proteins, so that most of the compounds are tissue-soluble. Only suspensions delay these tissue reactions and become encapsulated before they are absorbed, while the water-soluble ones are precipitated and react like insoluble compounds. After intramuscular injection some may be stored in the liver and other organs, but the greater portion is eliminated by the kidneys, liver and the intestine. Minute quantities have been traced to saliva, tears and sweat. It appears in the urine within 18 to 24 hours, and can be detected even after 20 to 30 days.

Kidneys—Stockton* claims that Bismuth Sodium Tartrate given intramuscularly acts as a powerful diuretic. It is in many respects superior to mercurial diuretics, being safe and effective. Its action is less sudden but more prolonged, and acts by mobilising salt in the tissues of the body and bringing it into the blood stream. The usual dose is 0.3 grm.

Toxic effects.—The earliest symptoms are a disagreeable taste, coated tongue, foul breath and a blue line along the margin of the gums. These are followed by loss of appetite, nausea, vomiting and diarrhoea with stomatitis, nephritis and enteritis. Occipital headache, restlessness, mental depression and tingling of the hands followed the use of a certain number of injections of bismogenol (basic bismuth salicylate). The urine contains albumin and casts. Weakness, slowness and inco-ordinate movements follow and may lead to tetanic convulsion. There may be complete paralysis and death. In severe forms of ulcerations of the mouth, cancrum oris may supervene.

* *Archives of Internal Medicine*, 1932, 1, 142.

Attention to oral hygiene and administration of sodium thio-sulphate control gingivitis and stomatitis which are most troublesome. Sometimes serious exfoliative dermatitis and rarely jaundice may appear.

Administration of large doses of subnitrate for radiological purposes gives rise to symptoms of poisoning due to the formation of nitrite in the large intestine by the reducing action of putrefactive faecal bacteria. The symptoms are methæmoglobinuria, cyanosis, diarrhoea, asphyxia and death from respiratory failure.

Resnik* reports a case of bismuth poisoning following the use in a fortnight of 5 to 7 oz. of subnitrate. The chief symptoms were a bluish black discoloration of the gums, which were swollen and inflamed; a similar discoloration of the tongue, most marked at the apex of the papillæ; a patchy, diffuse discoloration of the buccal mucosa; swelling and tenderness of the gland; moderate anæmia and basophilic stippling of the red cells, clinical picture closely resembling lead poisoning. Bismuth was detected in the urine. Recovery followed the withdrawal of the salt.

THERAPEUTICS

Externally.—Bismuth is a cosmetic, the oxychloride being preferred for this purpose, as it can be reduced to the finest powder. As a local sedative, astringent and antiseptic bismuth may be applied in the form of powder, lotion or ointment to chapped hands and nipples, irritable ulcers, intertrigo, herpes, eczema, etc. Bismuth salicylate, dermatol and many non-official derivatives may be used as substitutes for iodoform. Bismuth has been used as a bismuth-iodoform-paste (B.I.P.P.) in the treatment of tubercular sinuses, and fistulæ. It is injected into these and very good results have been obtained. The chief disadvantage is that both bismuth and iodoform may be absorbed and produce toxic symptoms, but the relative nontoxicity is due to the presence of paraffin which prevents their absorption. Ferrier's snuff checks coryza and chronic nasal catarrh.

Internally.—As a *gastric protective and sedative* bismuth salts are remarkably efficacious in all irritable and painful gastric disorders, such as catarrh, vomiting, indigestion, gastrodynia, pyrosis and ulcers, simple and malignant. The only drawback to their use is that they cause constipation. As an antacid the carbonate is generally combined with magnesium carbonate and bicarbonate of soda (see page 73). They should be given on an empty stomach so as to form a uniform coating over the mucous membrane. If the pain is intense they may be combined with morphine or belladonna, and if the gastric irritability is great, with hydrocyanic acid dilute.

As an *intestinal sedative and astringent* they are largely employed in all forms of diarrhoea, acute or chronic, either in children or adults. The salicylate is a useful remedy for children's diarrhoea due to the decomposition of food, because it has the properties of both bismuth and salicylic acid. Occasionally it may with advantage be combined with grey

*Bull. John Hopkins Hospital, May, 1926

powder. It has also been found very useful in summer and tubercular, enteric and lenteric diarrhœa, or cholera. Bismuth salts are most effective remedies in **mucous diarrhœa** and **dysentery**, and is often combined with castor oil (*see* page 350). In the last disease they may be given with Dover's powder to check the after diarrhœa.

Syphilis.—Sauton and Robert have shown that tartro-bismuthate of sodium and potassium is preventive and curative of fowl spirillosis as well as trypanosomiasis. Subsequently it has been found by French physicians to be of value in human syphilis. The advocates of this remedy maintain, that in doses which can be given intramuscularly safely, bismuth preparations have greater and more rapid therapeutic effect than mercury, that they may not be so quickly acting as arsenical preparations, but the effects are more permanent than those of arsenic. Small amounts are absorbed and enter the tissues where they possibly act as poison to the spirochætes, or at best inhibit their multiplication. Since it is not possible to introduce this drug in sufficient concentration to produce immediate result, the treatment is continued for a prolonged period in maximum tolerated concentration. There is no doubt that the organic arsenic compounds are more rapid in their effects and should get the preference in the primary stage of the disease. But all authorities agree that this requires to be supplemented by either mercury or bismuth. Some consider it superior to mercury in the treatment of congenital syphilis. They are of special value in those manifestations of the disease which are resistant to both mercury and arsenic. Since bismuth has been found in the cerebro-spinal fluid of treated cases and being neurotropic, favourable results are expected in the syphilis of the central nervous system. The results in general paralysis are disappointing, though it sometimes does good in tabetic crisis.

Lees summarises the value of bismuth in the treatment of syphilis as follows:—(1) It is more rapid in its effects than mercury but not so as the salvarsan group of drugs; (2) the surface lesions are influenced as rapidly as arsenobenzol, but more rapidly than mercury; (3) combined treatment with bismuth and arsenic is more potent than either given separately, and if the therapeutic doses are not exceeded the treatment has no untoward effect; (4) metallic bismuth in isotonic glucose solution is free from pain and other side effects, and is better tolerated in this form than either arsenic or mercury; (5) this treatment is of special value in cases intolerant to arsenic or mercury; (6) it is best used as an adjunct to other treatment and should not be used alone, even in very earliest cases, except in cases showing intolerance to arsenic or mercury.*

* *British Medical Journal*, Aug. 1927.

Other uses.—In association with the Rontgen rays, bismuth has been largely used for diagnostic purposes in connection with diseases of the *gastro-intestinal tract*, but its place has now been taken by barium sulphate (see page 107), which is less expensive and just as effective.

Prescribing hints.—As the less soluble preparations allay irritation better than the soluble ones, they are to be preferred when gastric or intestinal irritability is a prominent symptom. If they are given in a mixture they should be suspended by the compound tragacanth powder, and not by the mucilage of acacia, as the latter may convert the mixture into a jelly-like mass. Again the subnitrate should not be combined with any alkaline carbonates, for bismuth oxynitrate slowly parts with nitric acid in water and gives off carbonic acid. Neither should it be mixed with iodides in a mixture as it turns yellow from free iodine and from formation of iodide of bismuth. These salts should not be used with preparations containing tannin which form insoluble tannate of bismuth.

In the treatment of syphilis bismuth preparations should be used intramuscularly, the intravenous injection of the soluble salts is toxic and directly paralyses the heart and circulation, and is not used; moreover it is rapidly excreted. Subcutaneous injection causes too much irritation. The object is to form depots of slowly soluble compounds which may then be gradually and continuously absorbed. It has however the disadvantage of forming local fibrosis, when absorption of the drug from these depots becomes progressively impaired and finally arrested. Some patients show several of these nodules. This objection is less when potassium bismuth tartrate is used, as this is usually absorbed, or disappears from the site of injection in 2 to 4 weeks. The B.P. preparations are quite as good as any of the numerous compounds placed on the market. The soluble preparations are more quickly absorbed but are more toxic, while metallic bismuth and oxychloride are safe and absorbed at a uniform rate. *Injectio bismuthi* and *injectio bismuthi oxychloridi* are suspensions in glucose and are rapidly absorbed than *injectio bismuthi salicylatis* which is a suspension in oil. It is customary to give these injections at weekly intervals in doses of 0.2 to 0.24 gm. or 0.1 to 0.2 gm. at intervals of four days. The total amount given in a course varies from 2 to 3 gm. After ten to fifteen injections it is necessary to wait till it is absorbed before starting with the second course. A point midway between the ischial tuberosity and the posterior superior iliac spine is chosen and sterilised by iodine. The needle is then thrust perpendicularly into the muscle. See that no blood comes out of the needle before giving the injection.

A SENI T I XI UM

Arsenic Trioxide. (Arsen. Trioxid.)

Syn.—Arsenic ; White Arsenic ; Acidum Arseniosum.**Syn. I.V.**—*Sankia*, Hind. *Sanko*, Beng.**Source.**—Obtained by roasting certain arsenical ores. Contains not less than 99.8 p.c. As_2O_3 .**Characters.**—A heavy, white powder or irregular lumps having a vitreous fracture, containing frequently both transparent and opaque varieties. *Soluble* slowly in 65 parts of water, freely in acidulated water, or solutions of alkali hydroxides or carbonates, slightly in alcohol (90 p.c.).**Incompatibles.**—Lime water, iron salts, magnesia and astringents**B.P. Dose.**— $\frac{1}{8}$ to $\frac{1}{2}$ gr. or 0.001 to 0.005 grm.

OFFICIAL PREPARATION

1 **Liquor Arsenicalis.** **Syn.**—*Fowler's Solution*.—Contains 1 p.c. w/v of arsenic trioxide, or about $\frac{1}{2}$ gr. in 8 ms. **B.P. Dose**—2 to 8 ms. or 0.12 to 0.5 mil**A SENI T IIO I U**

Arsenic Triiodide. (Arsen. Triiod.)

Syn.—Arseni Iodidum.**Source.**—Obtained by combination of arsenic and iodine, and purifying the product by crystallisation.**Characters.**—Small, orange crystals. *Soluble* in 18 parts of water, in 42 parts of alcohol (90 p.c.), in ether, chloroform and in carbon disulphide.**B.P. Dose.**— $\frac{1}{16}$ to $\frac{1}{2}$ gr. or 0.004 to 0.016 grm.

OFFICIAL PREPARATION

1. **Liquor Arseni et Hydrargyri Iodidi.** **Syn.**—*Donovan's Solution*.—1 p.c. solution. Contains $\frac{1}{2}$ gr. of each salt in 15 ms. **B.P. Dose.**—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATIONS

1 **Ferri Arsenas**—A tasteless, amorphous greenish powder. *Dose*— $\frac{1}{16}$ to $\frac{1}{4}$ gr or 0.004 to 0.016 grm2 **Sodii Arsenas Anhydrosus**—A soluble white powder *Dose*— $\frac{1}{40}$ to $\frac{1}{10}$ gr or 0.0015 to 0.006 grm

PHARMACOLOGY

Externally.—Arsenic is a local irritant acting slowly on the tissues producing inflammation which may even cause sloughing. This irritant action is more marked on the denuded surface or mucous membrane. After prolonged application the cells die, but it is more destructive to pathological tissue than healthy cells.*Internally.*—In small therapeutic doses it increases the gastric vascularity and secretion, and thus improves appetite and digestion. In large doses it is a powerful gastrointestinal irritant, and causes severe inflammation of the whole digestive tract. The gastric mucous membrane becomes congested and swollen and even shows signs of hæmor-

rhage. It was formerly held that these symptoms were due to local action on the alimentary canal similar to that produced by strong acids or the caustic metals. They are, however, due to paralysis of the capillaries of the splanchnic area. As a result of this action there is exudation, œdema and increased peristalsis with watery stools which contain shreds of mucus and coagulated exudation forming the so-called rice water. Arsenic even when subcutaneously injected is excreted into the stomach. This view will not explain the fatty infiltration and cloudy swelling which are the specific effects of arsenic.

Blood.—The action of arsenic on the blood is not well understood, although it is used in some forms of anæmia. In normal person it diminishes the number of red cells though the hæmoglobin is unaffected, in fact it does not stimulate the production of red cells. The improvement may be due, as Stockman has suggested, to some specific effect on some undiscovered toxin or parasite, or as pointed out by Gunn to anti-hæmolytic action which protects the red corpuscles from destruction. Arsenic increases the leucoblastic elements of the bone marrow which becomes more vascular, and this may have some share in improving anæmia. Some hold that arsenic sets free some of the blood forming principles by causing destruction of a portion of the patient's liver.

Heart and circulation.—In isolated heart the amplitude is first increased and then diminished. Comparatively small doses directly paralyse the frog's heart making it slow, weak and irregular, which eventually stops in diastole. The mammalian heart is little affected, but in poisoning the muscles are directly depressed. The capillaries dilate enormously and the blood-pressure falls. This effect is due to the direct action of the drug on the capillary walls, specially those of the splanchnic area. Since the pressure falls even when the intestines are tied, it follows that besides the splanchnics other vessels are also dilated, the splanchnic vessels, however, are more susceptible to the action of arsenic than those of the rest of the body. The arsenites are more toxic than the arsenates and the inorganic preparations more than the organic ones.

Metabolism.—In minute doses administered for a long time arsenic enjoys the reputation of increasing growth and nutrition by checking oxidation. The condition of the skin improves, the bones become longer and more compact and there is increased vascularity of the bone-marrow. It is not clearly understood how these changes are brought about since the results of different observers have been different. While improvement in nutrition has been reported by some observers others like Stockman and Greig observed no change in the growth of animals under prolonged use. Small doses are supposed to increase the assimilatory pro-

cesses and help storage of proteins. Large doses produce effects similar to phosphorus but of a milder nature. Prolonged use lessens the activity of the liver and reduces the formation of glycogen, which may disappear entirely. The carbohydrate metabolism is stimulated so that a large amount of sugar is assimilated without producing glycosuria. Since there is inefficient oxidation, the intermediate product, lactic acid, appears in the blood causing partial acidosis. The liver becomes enlarged and the pressure in the bile duct prevents escape of bile into the duodenum, producing jaundice and allowing bile pigments to appear in the urine. There is increased protein breakdown and although the total nitrogen of the urine is not much altered, there is increased amount of urea, ammonia, leucin, tyrosin, etc. Fatty degeneration of the liver, kidneys, heart and muscles generally is evident. Binz and Schulz explain the action by supposing that it acts as a carrier of oxygen, which it receives and gives up, by transformation of arsenious to arsenic acid in the tissues and by the reduction of the arsenic into arsenious acid. This theory however does not explain all the effects of arsenic.

Nervous system.—Ordinarily no special action on the nervous system is elicited by arsenic. In acute poisoning no evidence of its action on the nervous system is observed as death takes place from gastro-intestinal irritation before any nervous symptoms can develop. Sometimes paralysis of the extremities appear with disturbances of sensation from central action, although they may be partially explained by the disturbances of nutrition. In chronic poisoning symptoms of peripheral neuritis develop with limited areas of paralysis.

Respiration.—We do not know much about its action on respiration except that habitual eaters of arsenic, such as the Styrian peasants, can undergo great exertion without much difficulty and distress of breathing.

Skin.—Arsenic has a marked effect on the nutrition of the skin, it improves the complexion and cutaneous nutrition, and increases the subcutaneous fat. It is eliminated with the sweat, and causes itching and eruptions, which may be erythematous, papular, pustular, furuncular, pigmentary or urticarial. These effects may be due either to some specific action produced by the drug upon the epithelium of the skin during excretion, or increase of lymph to the part. The most characteristic action is the darkening of the skin, "*arsenical melanosis*," which may vary from slight pigmentation to a deep brownish-red, and is due to deposition of some organic compound in the deeper layers of the corium.

Toleration.—Long continued use leads to tolerance, so that quantities which would otherwise cause toxic symptoms are taken without any ill-effects. The peasants of Styria take arsenic to improve their complexion and power for work and they can undergo extreme bodily exertion without

any respiratory distress. It is not known how this tolerance is established, although it is possible that long continued use may help formation of some antitoxin, or that the body is able to fix it in some non-toxic form. Some hold that absorption is so delayed that acute poisoning does not occur and in support of this view mention that arsenic eaters suffer from the symptoms of poisoning when the drug is administered in solution or hypodermically. It is evident that there is no true tolerance and that the body cells remain susceptible to arsenic. Housman attributes it to increased excretion. He has further shown that the corrosive action of arsenic on the gut is diminished by habituation.

Elimination.—It is excreted chiefly in the urine and to some extent in the faeces. A small percentage is also excreted in the bile, sweat, saliva, tears and milk. The excretion begins within two to eight hours after administration. Given by the mouth it is excreted by the intestine, while used hypodermically it is eliminated largely by the kidneys. Its elimination is very slow and incomplete and traces may be recovered two or three weeks after stoppage of its use. It is therefore cumulative. Less than 20 p.c. appears in the urine and faeces in the first 24 hours. The arsenic retained is distributed throughout the body, a considerable amount being stored in the liver and is slowly got rid of in the hair and epidermis where it may be found for months even after the drug has disappeared from the urine and faeces.

Acute toxic action.—Colicky pains, severe vomiting and purging, cramps of the legs, intense thirst, prostration and collapse are the prominent symptoms, which may be mistaken for those of cholera. At the *post-mortem* the stomach and intestine are found inflamed, with occasional patches of softening of the mucous membrane. *Fatty degeneration of the liver, kidneys, and heart* is found if the patient survives long enough. In fulminant cases there may be no symptom of gastro-enteritis, death takes place from collapse due to withdrawal of blood to the splanchnic area before enteritis develops.

The fatal dose varies, 0.1 to 0.3 grm. of trioxide is usually fatal.

Treatment. Emetics, apomorphine. The pump must be used with great caution. Moist peroxide of iron freshly prepared by mixing solution of ferric chloride with sodium or ammonium carbonate and straining rapidly through muslin, or dialysed iron in 1 oz. doses diluted, or better still ferri hydroxidum e magnesi oxido. Demulcents, and castor oil to clear the intestine, stimulants, hot-water bottles etc.

Chronic toxic action.—Chronic poisoning occurs amongst those who either handle arsenical pigments, inhale arsenical dust from wall-paper, dresses, etc., or consume wines* containing traces of arsenic. Loss of appetite, nausea, vomiting, colic, mild diarrhoea, oedema of the lower eyelids, conjunctivitis, swelling of the joints are the symptoms generally observed, when arsenic is continued long medicinally in large doses. Peripheral neuritis, muscular paralysis of the limbs, ataxic gait, muscular atrophy, bronzing and patchy pigmentation of the skin and darting pains in the limbs are also noticed in many cases of slow poisoning. Skin eruptions are a

*Peripheral neuritis was a marked symptom in an outbreak of arsenical poisoning in England, due to drinking contaminated beer

common accompaniment and are due to the direct action of the drug. Irritation of the mucous membranes of the eye, nose and larynx follows and is analogous to skin eruption.

THERAPEUTICS

Externally.—Arsenic was formerly extensively used as a caustic in the form of paste for destroying new growths, such as lupus, condyloma, epithelioma, warts, etc. Its use has been superseded by surgical measures, radium and deep X-ray.

Internally. Gastro-intestinal tract.—Dental arsenical paste is employed to destroy the tooth-pulp in caries of the tooth, before stopping. In minute doses *before* meals, arsenic may be given in irritative dyspepsia, vomiting of habitual drunkards, vomiting or diarrhœa excited by food and gastric neuralgia. For other diseases of the alimentary tract, it is given *after* food.

Lungs—Arsenic has been used in the treatment of asthma and its prolonged administration checks asthmatic fits. It has also been used in the treatment of phthisis where it appears to act as a general tonic and has no specific action on the tubercular lesion.

Malaria.—Arsenic is used in the treatment of malaria, and its value is more marked in chronic cases accompanied by anæmia and cachexia. Its effect in acute cases is not so marked as quinine, but given with iron and quinine after the acute stage, it is certainly of great value. In cases where quinine fails to effect a cure, a combination of quinine and arsenic will be found to yield better results (*see* page 455). The writer considers arsenic to be a useful remedy for arresting the paroxysmal febrile attacks of elephantiasis arabum, but it must be continued for a long time.

Nervous system.—In large doses arsenic is an old remedy for chorea, but its place has partly been taken by the salicylates. It is useful in those cases where the nervous elements are prominent. The disadvantages of giving arsenic in large doses are: (1) it sets up gastro-intestinal irritation; (2) it may cause severe neuritis. Children over 4 or 5 years of age can bear as large doses as adults.

Lymphomas.—In Hodgkin's disease (general lymphadenoma), no remedy is known to be of any use except arsenic. Large lymphomas are said to have been absorbed by the continued use of arsenic internally and hypodermically into the tumours.

Anæmia—Arsenic is used in pernicious anæmia where it improves the number of red blood corpuscles and the hæmoglobin, in leukæmia it is often used in large doses, but the beneficial effects of arsenic in these conditions appear to be only of a temporary nature. Arsenic is also useful in *microcytic anæmia* and in anæmia following malaria, specially when combined with iron. Some clinicians use it in chlorosis,

but it appears that beyond the general improvement of nutrition and lessening breathlessness and to a certain extent acting as a heart tonic, it has no specific action in chlorosis when used alone.

Skin.—Chronic skin diseases, especially scaly and papular varieties, are wonderfully benefited by arsenic. Psoriasis, lichen, chronic eczema, acne, pemphigus, etc., yield to it. It seems to act specially well in diseases affecting the epidermis rather than other portions of the skin.

Caution.—(1) Do not use arsenic during the inflammatory stage of any cutaneous disease.

(2) Always administer after food and well diluted, except where its local action on the stomach is desired.

(3) As soon as itching, smarting, or irritation of the conjunctivæ, œdema of the lower eyelids, pain on the pit of the stomach, or symptoms of neuritis are noticed, the dose must be reduced to one-fourth or one-fifth. If the irritation does not subside it must be further diminished, or stopped altogether.

(4) If the skin becomes irritated, a laxative may be given, rather than the treatment be stopped.

(5) For the radical cure of chronic skin disease it must be continued for some months after the final disappearance of eruptions.

(6) Children over 5 years of age can bear as large doses as adults. Old people bear it badly.

Prescribing hints --Solid arsenic is given in pill. Sometimes it is used hypodermically, as in multiple sarcomas, but with doubtful benefit. For prolonged use Fowler's solution is the best preparation, and the dose should be slowly increased to its therapeutical limit of tolerance. It is contra-indicated when gastric or intestinal irritation is present, such as nausea, loss of appetite, etc.

ORGANIC ARSENIC PREPARATIONS

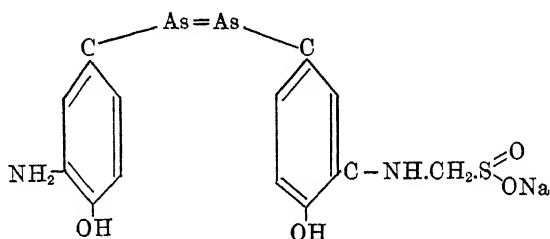
Within recent years these compounds have come to occupy an important position among the therapeutical agents for the treatment of several protozoal diseases, notably syphilis and trypanosomiasis. They belong to two groups, *viz.* *trivalent* and *pentavalent* compounds, in both of which the arsenic exists in non-ionisable form and therefore they can be given in large doses. They are less toxic than the inorganic salts, and do not possess the specific paralysing effect on the capillaries. They however do not produce their typical action immediately, but are slowly reduced in the body into ionic form by oxidation and other processes, when they become active. They are specially toxic to the invading parasite, though very little parasitocidal effect is seen *in vitro*, possibly they require the co-operation of the host to become parasitotropic.

1. Trivalent Compounds

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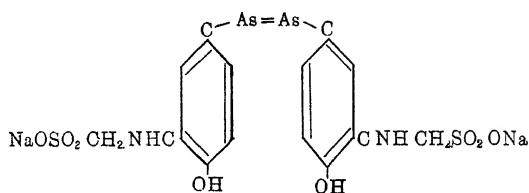
(Neoarsphenamin.)

Neoarsphenamine

Syn—Novarsenobenzol; Neosalvarsan; Novarsenobenzene; 914.**Source**.—May be prepared by treating 3:3'-diamino-4:4'-dihydroxyarsenobenzene with sodium formaldehydesulphoxylate. It is distributed in hermetically sealed glass phials, from which air has been excluded, or replaced by an inert gas. Contains about 20 p.c. arsenic.**Characters**.—A yellow, dry powder, freely mobile in contact with glass surface; odour, none, except that due to traces of ether or alcohol.**Soluble** in water, insoluble in dehydrated alcohol. A 1 p.c. w/v aqueous solution is neutral, or slightly alkaline, to litmus.**Storage**.—It should be kept at a temperature below 15°C. It should not be used if it becomes darker in colour.**B.P. Dose**.— $2\frac{1}{2}$ to 14 grs. or 0.15 to 0.9 gm. (intravenous injection).**SULP A SP ENA INA**

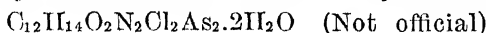
(Sulpharsphenamin.)

Sulpharsphenamine

Syn.—Sulpharsenobenzene; "Sulfarsenol."**Source**.—Prepared by treating 3:3'-diamino-4:4'-dihydroxyarsenobenzene dihydrochloride with formaldehyde and sodium hydrogen sulphite. Supplied in sealed glass phials like neoarsphenamine. Contains about 20 p.c. arsenic.**Characters**.—A yellow, dry powder, freely mobile in contact with glass surface; no odour, except of alcohol or ether. **Soluble** in water; insoluble in alcohol (95 p.c.), and in ether.**Storage**.—It should be kept at a temperature below 15°C. It should not be used if it becomes darker in colour.**B.P. Dose**.— $1\frac{1}{2}$ to 10 grs. or 0.1 to 0.6 gm. (subcutaneous or intramuscular injection).

ARSPHENAMINA, U.S.P.

Dioxy-diamino-arseno-benzene Hydrochloride

**Syn.**—Arsenobenzol; Salvarsan; 606.

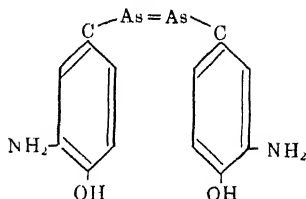
Characters.—A light yellow powder, odourless or has a slight odour. Hygroscopic. In the dry state or in solution it is oxidised by exposure to the air, becoming darker and more toxic. Soluble in water, alcohol, and glycerm. Contains not less than 30 p.c. of arsenic.

N.B.—Preserve in sealed colourless glass tubes from which air has been excluded either by production of a vacuum or by displacement with a non-oxidisable gas.

Dose, U.S.P.—Intravenous, $6\frac{1}{2}$ gr. or 0.4 gm.

Preparation of solution.—*Intramuscular.* Place the required salvarsan in a small porcelain dish and rub it with 9 to 10 drops of sodium hydroxide solution 15 p.c. by weight, then add (carefully rubbing all the time with a glass rod) drop by drop required amount of fresh distilled water, about 5 to 10 c.c. Neutralise the solution by the addition of sodium hydroxide or dilute hydrochloric acid.

Intravenous.—Place 30 to 40 c.c. physiological salt solution in a 300 c.c. stoppered bottle, add to this 0.6 gm. of salvarsan. Dissolve it by thorough shaking, add 23 drops of 15 p.c. sodium hydroxide solution. A precipitate forms which quickly re-dissolves. Dilute the remaining clear yellow solution to 300 c.c. with normal saline solution. Each 50 c.c. is equal to 0.1 gm. Therefore 150 c.c. form the average dose for women and 200 c.c. for men.

**NON-OFFICIAL PREPARATION**

1 **Arsphenamina Argentica, B.P.C.** *Syn.*—Silver Salvarsan, Silver Arspenamine.—Contains 18 to 21 p.c. of arsenic and 12 to 13 p.c. of silver. 0.1 gm. corresponds to about 0.2 gm. of arspenamine or 0.3 gm. of neoarsphenamine. Valuable in syphilis of the central nervous system.

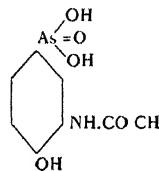
Dose.— $1\frac{1}{2}$ to 10 grs. or 0.1 to 0.6 gm. in 1 p.c. solution intravenously, at an interval of not less than 4 days for men. 0.1 gm. equals 0.3 gm. of neosalvarsan.

2. Pentavalent Compounds**ACETARSOL****Acetarsol****Syn.**—Acotarsonic; "Stovarsol".

Source.—It is 3-acetylamino-4-hydroxyphenyl-arsonic acid. Contains 27.0 to 27.4 p.c. As.

Characters.—A white, crystalline powder. Almost insoluble in cold water, moderately soluble in boiling water, insoluble in alcohol (95 p.c.), and in dilute acids; soluble in dilute alkalis.

B.P. Dose.—1 to 4 grs. or 0.06 to 0.25 gm.

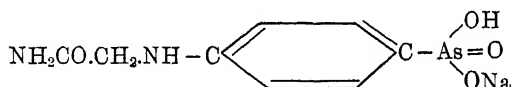
**TRYPARSAMIDU**

Tryparsamide. (Tryparsamid.)

Source.—It is sodium N-phenylglycineamide-p-arsenate. Contains 25.1 to 25.5 p.c. of As in organic combination.

Characters.—A colourless, crystalline powder; odourless. Freely

soluble in water; insoluble, or only slightly soluble in alcohol (95 p.c.) in ether, in chloroform, and in benzene.



Storage.—It should be kept in a small well-closed container, protected from light, and stored in a cool place.

B.P. Dose.—15 to 30 grs. or 1 to 2 grms. *By subcutaneous, intramuscular or intravenous injection.*

NON-OFFICIAL PREPARATIONS

1 **Acidum Cacodylicum**—It is dimethyl-arsonic acid, soluble 2 in 1 of water and 1 in 4 of alcohol (90 p.c.) Its effects are more or less like inorganic salt to which it is partly reduced in the body. Changes take place slowly and the action is prolonged. It imparts an odour of garlic in the urine, sweat and breath. *Dose* — $\frac{1}{2}$ to 2 gr. or 0.03 to 0.12 gm.

2 **Ferri Cacodylas**—A yellowish, amorphous powder, soluble 1 in 15 of water. *Dose* — $\frac{1}{4}$ to $\frac{1}{2}$ gr. or 0.016 to 0.03 gm. in pills three times daily $\frac{3}{4}$ gr (0.05 gm.) *hypodermically* daily. Chiefly used in *anæmia* and *chlorosis*.

3 **Guaiacol Cacodylas**. *Syn*—*Cacodylacol*—Chiefly used in *tuberculosis*. *Dose* — $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 gm. *per os*, or dissolved in sterile oil *hypodermically*.

4 **Strychninæ Cacodylas**.—A white crystalline powder slightly soluble in water. *Dose* — $\frac{1}{30}$ to $\frac{1}{10}$ gr. or 0.002 to 0.006 gm.

5 **Sodii Cacodylas, U.S.P.**—*Sodium Dimethylarsonate*—In white, colourless, deliquescent prisms, or as granular powder. It is used in all cases in which arsenic has been used, and is valuable in chronic skin affections and *phthisis*. Given in doses of 1 to 2 grs. *intramuscularly*. Therefore it can be used with less danger of upsetting the stomach. It may also be given in pill form. *Dose*—*Hypodermically*, $\frac{1}{2}$ to 1 gr. (0.03 to 0.06 gm.), but it may be increased to 3 grs. as *maximum single dose*, and as *maximum dose* in 24 hours. If given by mouth or per rectum it may cause renal congestion with a fall of urinary secretion. *Dose, U.S.P.*—1 gr. or 0.06 gm.

6 **Di-sodium Methylarsonate**. *Syn*—*Arrhenal*, "*New Cacodyl*"—Soluble 1 in 1 of water and sparingly in alcohol. Its arsenic content is 27.35 p.c. Its uses are the same as sodium cacodylate. *Dose*— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 gm. by mouth, or hypodermically, the *maximum dose* (single or in 24 hours) being 3 grs.

7 **Sodii Aminarsonas, B.P.C.** *Syn*—*Soamin*, *Atoxyl*, *Arsamin*—A white crystalline powder with a saline taste, soluble 1 in 3 of water at body temperature. Solutions, which should be freshly prepared, may be sterilised by boiling five minutes without becoming decomposed. Its arsenic content should be at least 22.8 p.c.

Dose—*Per mouth* — $\frac{3}{4}$ to 3 gr. or 0.06 to 0.2 gm. twice daily after food. *Maximum daily dose*—3 grs. *Hypodermically*, 1 to 3 grs. or 0.06 to 0.2 gm. *intramuscularly* high up into upper third of buttock on alternate days. The salt should be dissolved in sterile water. *The maximum of 3 grs. cannot be exceeded with safety*

USES

Atoxyl has been used in *syphilis* intramuscularly, and provided the precautions to be hereafter noted are attended to, no bad effects or signs of toxicity should follow.

In *trypanosomiasis*—human and animal—soamin has been largely used with some success, but in many cases recurrence of the disease has occurred.

Soamin and the cacodylates have been used with success in *anæmia*, locomotor ataxy, relapsing fever, pellagra, cerebro-spinal meningitis, tuberculosis and chronic skin diseases (psoriasis and lichen).

Hypodermically it has been found to be of great value in *bronchial*

asthma with eosinophilia* in 1 gr. doses, increased to 3 grs. given twice a week. Administration of alkalies helps its action.

Precautions.—Several cases are on record of blindness due to optic atrophy following its use. This possibly was due to an unsafe dosage being used, but as idiosyncrasy and previous optic degeneration are important factors, it is necessary to proceed with caution when using the remedy. The following are points to which attention should be paid:—

1. Always examine the retina and the disc for degenerative changes before commencing a course of treatment, and if normal, periodically test the vision and look for any contraction of the fields—if any contraction is noticed stop use of the remedy.

2. In cases of renal and hepatic disease, and in arteriosclerosis, do not use the drug, and only use it with great caution for this reason in old patients.

3. When 100 grs. have been given stop for four weeks.

The earliest toxic symptoms to be carefully watched for are insomnia, gastric pain and haziness of vision.

8 **Arsacetin** *Syn*—*Sodium Acetyl-p-aminophenylarsionate*—It has been used in syphilis and *trypanosomiasis*. It is also useful in *anemias*, in such cases however a smaller dose, viz. 0.1 gm. to 0.5 gm., should be given subcutaneously. As with atoxyl caution in its use is to be recommended, as cases of blindness have been reported after its use.

Dose— $\frac{1}{4}$ to 3 grs. or 0.05 to 0.3 gm. per os, three to four times daily. *Intramuscularly* a maximum of 3 grs. in 10 p.c. solution should not be exceeded.

PHARMACOLOGY OF ARSENOBENZOL DERIVATIVES

The introduction of salvarsan as a remedy for syphilis is the direct result of the chemotherapeutic studies of Ehrlich, who suggested a parasitocidal action of the drug. Certain side chains of the drug possess a selective affinity for certain side chains of the protoplasm of the spirochaete, and the drug kills the germs at a concentration harmless to the tissues of the host. This theory however is open to doubt. These organic compounds undergo certain changes in the body tissues when they exert an action either on the parasites or on the host. The arsenic in arsenobenzol exists in trivalent form; and Voegtlin has suggested that it is inactive in this form but becomes active when it is partly oxidised in the tissues. It circulates in the blood in the colloidal form and is very soon deposited in the tissues. It is believed that salvarsan is deposited in different organs in relatively non-toxic form and that it is doled out in more active form, which acts more powerfully on the *spirochaetes*.

The mode of action of these compounds appears to be an indirect one, and the presence of arsenic within the reticulo-endothelial cells has actually been demonstrated,† while splenectomy experiments in spirochætal infections have established that infections held in check in animals break into acute manifestations in splenectomised animals and that treatment of these with specific drugs is less effective than in non-splenectomised animals. In fact there is evidence to

* Ghosh, *Glasgow Medical Journal*, 1919.

† Jimenez de Asua and Kuhn, 1928.

show that the mortality rate is increased and the cure rate is decreased after splenectomy, and that an intact reticulo-endothelial system is necessary for the full functioning of the chemotherapeutic compounds of arsenic.

Given intravenously in increasing doses, salvarsan causes dilatation of the heart, rise of pulmonary pressure and a slow fall of systemic pressure. The heart is depressed depending on the concentration and reaction of the solution used, acid solutions being specially toxic.

Absorption and elimination.—Absorption is very slow even when given intravenously. Very little is absorbed by the rectum. With neoarsphenamine the kidneys contain the most arsenic, then the spleen, the liver, thyroid, adrenals, heart, muscles, etc. Although after long continued use large quantities may be stored in the different organs of the body, it is doubtful whether this arsenic is therapeutically active, or capable of being rendered so after reabsorption into the blood. Wechsellmann, Lockemann and Ulrich have shown that the stored arsenic is therapeutically inactive, it is only during the short period when the arsenic is in the blood that its maximum effect is exerted.

It is broken down in the body and excreted in the urine and faeces as ionised arsenic. The percentage of arsenic after salvarsan given intravenously is greater in the faeces than in the urine, although it appears in the urine within a few hours, and not till the third or fourth day that it is found in the stool. The greater part found in the stool is due to rapid elimination through the bile which has a high arsenic content. Excretion is slow after intramuscular injection, and the maximum quantity eliminated in 24 hours after an intravenous injection of salvarsan is about 10 mg, i.e. about 3 p.c. of arsenic contained in 0.9 gm. The excretion is said to be hastened by the administration of potassium iodide. The pentavalent compounds are excreted more rapidly, about 85 p.c. being eliminated within 24 hours. The rate of excretion shows wide individual variation which accounts for the difference in toxicity and therapeutic activity. Damage to the kidneys causes considerable variation in the rate of excretion.

After an intravenous injection the drug must circulate through the brain and the cord, but whether it penetrates the cerebro-spinal fluid has received much attention. While some observers found no trace of arsenic in the brain after intravenous injections of arsphenamine, others (Fordyce, Rosen and Myers) detected in more than 80 p.c. of cases, at least during the period of treatment.

Toxic symptoms and other side effects :—

As a rule few cases show any symptoms of poisoning when arsphenamine is injected. According to individual variation, cases have been observed where symptoms of poisoning appeared, and these effects varied from simple disturbance to grave and even fatal issues.

Some of these cases were no doubt due to faulty technique, others from some form of arsenical poisoning, while a few were due to alteration in the colloidal equilibrium of the blood following an injection of a large bulk of fluid. The symptoms may be grouped as follows:—

1 *Immediate reactions*.—In about half to five per cent. of cases severe toxic symptoms appear within a few minutes. Although alarming they are rarely fatal. The face becomes flushed, the conjunctiva injected, tongue and eyelids become cedematous. Nausea, vomiting, profuse perspiration, cough, dyspnoea and precordial pain are often present. If stomatitis is present there may be pain in the gums and teeth, or in more severe forms the tongue and lips may become swollen. These symptoms are known as *nitritoid reaction*. The exact cause of this immediate reaction is still a matter of speculation. They are common with patients with tubercular lesions (Stokes), or when a large volume of fluid is injected, as with salvarsan. They are probably due to some alteration in some blood proteins (flocculation and agglutination), or to the presence in the blood of the breakdown products of spirochaetes, or to liberation of a histamine like substance.

2 *Early toxic symptoms*.—These generally appear within a few hours after administration and are characterised by febrile reaction with chill, nausea and vomiting. There may be severe pains in the body. Kidneys show evidences of damage with albumin and casts. As a rule these may be temporary and the symptoms disappear with the stoppage of treatment. Urticarial and other forms of skin eruptions may appear (*exfoliative dermatitis*). These generally appear after about a week and may be very severe. Although sulpharsphenamine is supposed not to cause skin eruption, the writer had a severe case of exfoliative dermatitis following the use of this preparation.

Occasionally the syphilitic process may show an increase in an acute form after the injection. There may be an exacerbation of a syphilitic keratitis resulting in blindness, or deafness, or development of other types of acute lesion of the central nervous system. If the secondary skin lesions are present they become erythematous, swell up and show an increase of secretion from the ulcers. This phenomenon, which is known as *Herxheimer reaction*, comes on suddenly and is due to the poisonous action of the proteins set free from the spirochaetes. The appearance of any of these symptoms implies that the treatment should be stopped.

3 *Severe late reactions*.—Occasionally severe and even fatal symptoms appear a few days after administration. In addition to some of the symptoms already described, the cerebrum and the liver are involved.

The cerebral symptoms (*arsphenamine encephalitis*) appear after large doses, or when the ordinary doses have been given too quickly. The onset is sudden, the symptoms being headache, vomiting, dyspnoea, epileptiform convulsion with clonic spasms, followed by unconsciousness, suppression of urine, dilated pupil, coma and death, generally forty-eight hours after the onset of the symptoms. Hemorrhagic encephalitis occurs during the secondary stage, as a rule after the second injection.

Jaundice appears in the course of treatment and may start suddenly, may be intense and may end fatally. Three types of jaundice are usually found; they are:—

(a) *Early jaundice*, usually commences within a few hours, may appear suddenly, or after subsequent injections.

(b) *Late jaundice* is a more serious disorder and appears several weeks to several months after termination of a course of injections. Unless followed by acute yellow atrophy of the liver, recovery takes place. Liver may be enlarged, with bile and traces of albumin in the urine.

(c) *Acute yellow atrophy of the liver* is a more serious complication and appears some weeks after the end of a course of treatment.

The following factors influence toxicity:—(1) Abnormal toxicity of the drug; (2) errors in technique; and (3) susceptibility of the patient; and are avoided by (1) using a reliable preparation; (2) following the same technique in the preparation and administration of the drug; (3) a preliminary examination of the patient for possible visceral disease; and (4) watching the patient during the whole course of treatment.

Treatment of poisoning.—Since the symptoms of nitritoid reaction resemble anaphylaxis and nitrite poisoning, adrenaline and atropine are suitable remedies. It can also be prevented by giving 20 to 30 ms. of spiritus ammoniæ aromaticus in a little water five minutes before the injection, which is given very slowly. By giving one-tenth of the dose an hour before the remainder is given, the toxic symptoms may be averted. The patient should be carefully watched for any of the late toxic symptoms during a course of treatment and if any appear, further treatment should be suspended. Nephritis and other symptoms are treated on general lines. Sodium thiosulphate is useful in arsenical dermatitis (*see* page 86).

For *encephalitis*, Schamberg and Wright recommend the following:—Bed; spinal puncture, withdrawing 50 c.c. liquid; venesection, withdrawing 60 to 100 c.c. blood; thorough purging; large doses of bicarbonate of soda; injection of adrenaline, 5 ms. every four hours by day; oxygen inhalation for anoxæmia of the brain.

THERAPEUTICS

These preparations are largely used in certain types of protozoal and spirochætal infections, and are of special value in syphilis, Vincent's angina, yaws, etc., and good results have been reported in relapsing fever and rat-bite fever. A single injection of arsenobenzol or any of the derivatives will cause the spirochætes to disappear in a few hours from the chancre, and since a single dose will not reach all the parasites, the injections are repeated. After three injections the Wassermann reaction if positive becomes negative in most cases, but the improvement is not permanent, for after some weeks or months the reaction reappears and the symptoms of secondary syphilis begin to appear. It is therefore necessary that mercury or bismuth should be given after these injections and continued on the usual lines. The advantage of using arsenobenzol is the rapidity of its action, whereas the concentration required to sterilise the system with mercury is obtained after several days or weeks. Therefore after the immediate action has been obtained by the use of arsenic the treatment should be supplemented by the slow and prolonged action of mercury or bismuth. If proper treatment is adopted early during the primary lesion it will prevent secondary symptoms and effect a definite cure.

In the *secondary stage* with definite serum reaction, it will cause disappearance of the mucous lesions of the mouth and throat, and the healing of the skin rashes within a short time. In the *tertiary stage* the treatment should be com-

bined with courses of iodide. During pregnancy the injections of both neoarsphenamine and bismuth should be given, but in small doses, at the same time the kidneys should be watched to avoid developing nephritis.

The modern conception of the treatment of syphilis with arsenobenzol compounds is not to use a large dose to produce a high concentration of the drug in the blood for a limited period, but to maintain a moderate concentration for a prolonged period, by giving a series of injections in moderate doses instead of a single large dose. It has therefore been found necessary to give intramuscular injections more frequently so as to maintain a moderate concentration of arsenic for a prolonged period to effect complete recovery.

Some cases of syphilis do not improve under arsenobenzol and Ehrlich suggested that the failure was due to the parasites inhabiting in out of the way parts of the body, *e.g.* cerebro-spinal fluid, which the drug could not reach. After an injection most of the parasites in the blood stream are killed, but a few surviving ones slowly multiply and reinfect the whole system.

In the treatment of syphilis arsenobenzol is the drug of choice in early cases (chancre and secondary manifestations) affecting young healthy persons. Neoarsphenamine is preferred for elderly people, pregnant women, children and patients with cardiac, renal and other complications. Silver salvarsan is useful in neurosyphilis, extensive gummatous ulcerations and anaemia. But since the preparation of the solution of salvarsan is complicated, and therefore not suited for routine use, and its use was followed by a large number of accidents from errors in technique, neoarsphenamine has practically replaced it and is extensively used.

Salvarsan and neoarsphenamine have been used in malaria, yellow fever and human trypanosomiasis, but the results have not been encouraging.

Cerebrospinal syphilis should be treated with neoarsphenamine and bismuth, or salvarsanised serum may be administered fortnightly by intraspinal or intracisternal injections. Many syphilologists are however doubtful regarding the value of this treatment in cerebrospinal syphilis. Since tryparsamide has the power of penetrating the central nervous system more readily than other arsenical preparations, it has been used in neurosyphilis, but it has little power in killing spirochaetes and is not of any value in either primary or secondary stages, or against gumma. It has not proved successful in the treatment of early manifestations of cerebro-spinal syphilis, but gives good results in disseminated sclerosis when given before irreparable damage of the nerve cells have resulted and may be combined with malaria treatment. It is said to possess remarkable power of reinforcing processes of natural resistance

and promoting recuperation. It is valuable in human trypanosomiasis and has been used in filarial infection and chyluria with some success (see page 511).

Acetarsol has been used in yaws with some success, but the results were disappointing in trypanosomiasis, syphilis and filarial infections. It is active when given by the mouth.

Contra-indications.—(1) The injection should never be given on a full stomach, or when the blood-pressure is high. (2) It should not be given to persons suffering from hepatic disorders, chronic renal disease (of non-syphilitic origin), diabetes, or chronic myocardial degeneration, or to cases exhibiting evidences of recent endocarditis. (3) Owing to the congestive action of this drug it should not be used in cases with signs of active pulmonary tuberculosis, fetid bronchiectasis, or serious lung disease. (4) Patients whose vessels are atheromatous or who have suffered from cerebral hæmorrhage are also bad subjects for salvarsan. (5) Persons showing special idiosyncrasy to arsenic. (6) Persons suffering from non-syphilitic retinal diseases or affections of the optic nerve. (7) Advanced cerebral mischief and cachexia.

Method of administration.—Solution of arsenobenzol or novarsenobenzol given subcutaneously produce local irritation and inflammation. These effects are due partly to the drug and partly to the reaction of the solution, acid solutions cause severe and persistent pain, while alkaline solutions produce corrosion, ulceration and even gangrene. Neoarsphenamine though forms a neutral solution also produces severe pain, inflammation and fibrosis. Rectal administration has also been suggested but is not so effective. The usual method is the intravenous route. It is practically painless, and there is seldom objectionable local effects at the point of injection; if any should arise it may be ascribed to faulty technique. Moreover the time spent in bed is greatly reduced by this method. Whatever method is used strictest asepsis must be maintained. These injections should be followed by mercurial treatment, and usually injections of calomel or mercurial cream are given. When intensive treatment is required, a series of six intravenous injections, once a week, constitutes a course. But usually three injections are given at fortnightly intervals. The highest dose of salvarsan for a healthy adult man of average weight is 0.5 grm. intravenously, and 0.4 grm. for a woman. For a child ten pounds in weight the first dose should not exceed 0.01 grm. The maximum dose for a healthy adult Indian is somewhat lower, preferably 0.4 grm. of salvarsan for a man and 0.3 grm. for a woman. The dose of neoarsphenamine is greater than salvarsan in the proportion of 3 to 2, *i.e.* 0.6 grm. of neoarsphenamine equals 0.4 grm. of salvarsan. The dose should always be varied with the strength and condition of the patient. It has been found that smaller

doses frequently repeated give as good results as full doses and are less dangerous to the patient

Injection of Salvarsanised Serum.—Since very little arsenic passes into the central nervous system, intravenous use of salvarsan is not very useful in cerebrospinal syphilis. It has therefore been suggested that in these cases salvarsanised serum may be injected directly into the spinal canal. The results have been rather hopeful specially in the treatment of tabes.

Swift-Ellis Method.—The patient is given an ordinary dose of salvarsan or neo-salvarsan intravenously, and after an hour 40 c.c. of blood is withdrawn from a vein, which is allowed to clot and left for 24 hours on ice; 12 to 15 c.c. of serum is then drawn off and centrifuged. This serum contains about 0.01 mg. of salvarsan per c.c. It is heated to 56°C. for half an hour. This may be diluted with normal saline to make 30 c.c. and injected by lumbar puncture, an equal volume of cerebro-spinal fluid being first withdrawn. The injections are safe and may be repeated after two weeks.

POTASSII IODIDUM

(Pot. Iod.)

Potassium Iodide. KI

Source.—Obtained by the action of excess of iodine on a solution of potassium hydroxide, evaporating to dryness, fusing with charcoal, and purifying by crystallisation from water. Contains not less than 99 p.c. of potassium iodide.

Characters.—Colourless, transparent or somewhat opaque, crystals, or a white granular powder. Odourless; taste, saline, slightly bitter. *Soluble* in 0.7 parts of water, in 12 parts of alcohol (90 p.c.), in 2 parts of glycerin.

Incompatibles. Bismuth subnitrate, spiritus atheris nitrosi, solutions of ferric salts, dilute hydrochloric acid, liq. strych. hydrochlor., potassium chlorate, alkaloidal salts, and substances containing starch.

B.P. Dose —5 to 30 grs. or 0.3 to 2 grm.

SODII IODIDUM

(Sod. Iod.)

Sodium Iodide. NaI

Source.—Prepared from iodine and a solution of sodium hydroxide by a process similar to that adopted in making potassium iodide, the salt being crystallised at a temperature not less than 20°C. Contains not less than 99 p.c. of pure sodium iodide.

Characters.—A white, crystalline powder, deliquescent, having a saline and somewhat bitter taste. *Solubility*—Less than 1 part of water, 1 in 3 of alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.

NON-OFFICIAL PREPARATION

1 **Ammonii Iodidum.**—In minute colourless cubical crystals, or as white granular powder. Odourless, with a sharp saline taste. Very hygroscopic. Becomes yellow or brownish when exposed to air and light. *Dose* —2 to 6 grs. or 0.12 to 0.4 grm.

PHARMACOLOGY OF IODIDES

Internally.—The action of iodides is identical with that of iodine, except that these are less irritant to the gastro-

intestinal tract, and are therefore used in preference to iodine. Large doses cause irritation of the stomach and give rise to nausea and vomiting if used in concentrated solution.

Iodides are absorbed by the intestine and circulate in the blood as iodide through which it penetrates the different tissues of the body. The acid in the stomach may liberate highly irritating iodine. They are excreted with the saliva within a short time and give a metallic taste in the mouth. In large doses they produce a group of symptoms known as **iodism**. Besides the characteristic action of iodine they increase the secretion of bronchial glands during elimination through the respiratory mucous membrane, producing a flow of thin mucus, and liquefying tenacious secretion. Potassium iodide tends to lessen viscosity of the blood, dilate peripheral arterioles and reduce irritability of the heart without affecting its contractility.

They are diuretics, and are more powerful than chlorides. They act possibly by diminishing reabsorption from the tubules.

Excretion of lead and mercury fixed by the body is made rapid by potassium iodide. It forms insoluble, unabsorbable and non-poisonous lead iodide.

As the spirochaetes of syphilis are not killed by the application of iodide to a syphilitic lesion, it does not act as a parasiticide. The specific effects in the tertiary stage are exerted not on the parasites but upon the tissues in which the parasites live and which have reacted to their presence by the formation of gumma. These dissolve under the action of iodides. They combine with antitrypsin which normally prevent the resolution of necrotic tissue and set free proteolytic ferments which digest and absorb gummatous tissue.

Iodine is contained in the form of thyroxine in the thyroid gland, and administration of iodine or iodides increases the iodine content of the gland with corresponding increase of its activity.

Elimination.—Iodides are rapidly eliminated mainly by the urine, but partly also by the saliva, gastric juice, sweat, milk, and other secretions and body fluids and effusions. Seventy-five per cent. of the dose appears in the urine within twentyfour hours. The remainder may remain in organic combination in the body. Swift reported that iodine was not found in the cerebro-spinal fluid even after very large doses given by the mouth. Later Campbell and Snodgrass demonstrated iodine in the same fluid after oral use, and in larger amount after intravenous use.

Untoward effects.—Iodides sometimes give rise to certain symptoms either when continued for a long time in large doses or even with small doses due to idiosyncrasy. They are manifestations of irritative phenomena of the skin and the mucous membranes.

Skin.—In escaping through the skin they produce cutaneous eruptions, vesicular, bullous or hæmorrhagic, starting from the papillary layers and not from the sweat glands. All these skin reactions are due to the iodine set free in the skin glands by oxidation. Serious eruptions usually occur in patients with low vitality, and in those with chronic nephritis. Cleanliness of the skin and small doses of arsenic are the best prophylactics known at present

Mucous membranes.—The mucous membranes of the nose, throat, bronchi, conjunctiva, etc., are irritated by iodides giving rise to symptoms of iodism. There is running of the nose, œdema around the eyelids, sneezing, and headache, the symptoms resembling acute cold or influenza. Sometimes there may be œdema of the glottis with swelling of the parotid glands, a metallic taste in the mouth, loss of appetite, furred tongue, and salivation; while vomiting and diarrhœa may appear in more severe cases. Sometimes the symptoms disappear after the dose is increased, and are more common when the excretion is interfered with as in those suffering from nephritis, and disappear with the stoppage of the drug. The cause of these symptoms is not clearly understood. They are not due to liberation of iodine, nor to anaphylaxis, but are supposed to be due to alteration in the colloid equilibrium (Sollmann). It has been shown that intravenous injection of iodides alters the surface relation of the blood, and that these produce œdema from altered colloid-water affinity.

Treatment.—Carbonate of ammonium, sp. ammon. aromat., or bicarbonate of potassium controls iodism. Fowler's solution prevents skin eruptions. Calcium lactate is also used.

THE THERAPEUTICS OF IODIDES

Internally.—Iodides are employed in the same class of diseases where iodine is indicated but the following deserve a special notice:—

Respiratory passage.—As the iodides liquefy the phlegm and help expectoration, they are used in bronchitis, broncho-pneumonia and pneumonia. But since iodides produce hyperæmia and excite secretion of the respiratory mucous membrane, they are contra-indicated in acute bronchitis and other acute forms of respiratory troubles, *e. g.* in the early stage of pneumonia. It is helpful when the condition is chronic and the sputum more tenacious, as for instance in asthma and asthmatic bronchitis. Although they have no action on the bronchial muscles they are used in bronchial asthma in 5 to 10 gr doses, often with benefit. In pleurisy they help absorption of pleuritic fluid. In pulmonary tuberculosis they increase both the cough and expectoration and in some cases may accelerate hæmoptysis. By breaking the tubercular nodules they cause fresh infection by freeing the bacilli.

Heart and circulation—Iodides are used to absorb the effusion in pericarditis, and the deposits over the valves. They are extremely valuable in all conditions of the heart and the vessels following tertiary manifestations of syphilis. They often give relief to pain of aneurism. Prolonged use sometimes lowers the blood-pressure, but as a rule fails unless of syphilitic origin. It is believed that it helps to bring the pressure down by its action on the carotid sinus (page 285) provided there is sclerosis of the sinus. Beneficial results have been obtained in angina by giving iodine and iodides intravenously, and by subcutaneous injections of CO_2 ; both may be used either alternately or simultaneously. It is a valuable remedy in arterio-sclerosis and Stockman has suggested that the value of this drug is due to production of a large amount of thyroxin.

Brain.—It has been used in hydrocephalus, but only acts as a palliative. In meningitis and in cerebral lesions of syphilis, a combination with bromide and mercury is the time-honoured treatment.

Skin.—Many syphilitic cutaneous diseases are sometimes cured by full doses of iodides.

Scrofula.—The iodides, especially syrupus ferri iodidi, either alone or with cod-liver oil, have a remarkable effect in tuberculosis when the glands are affected.

Syphilis.—Although iodides have no toxic effects on treponema, sodium iodide has given good results in locomotor ataxy given intravenously (1 to 3 grm. in 10 p.c. solution). They are of immense value in tertiary syphilis, or rather in the manifestations of untreated syphilis which go to the tertiary stage. Periostitis, nodes, gummata, syphilitic deposits in the brain and other organs disappear with remarkable rapidity. Success depends upon boldly pushing the drug in doses of 20 to 40 grs. or even 60 grs. three times a day. They sometimes do good in the secondary stage specially when combined with mercury. They have no effect in primary stage, but are efficacious in congenital syphilis.

Goitre.—Iodine or iodides in small doses (2 grs. daily) sometimes produce good results in simple hypertrophic goitre and have been used both for prevention and treatment. But the patient requires to be constantly watched to prevent the symptoms of hyperthyroidism which may follow if the dose is large and used for a prolonged period. In Graves' disease its use has proved beneficial in reducing the metabolic rate prior to partial thyroidectomy.

Large doses are of great value in actinomycosis or sporotrichosis in 60 to 120 grs. given daily.

Metallic poisons.—Potassium iodide eliminates lead and mercury and other metallic poisons from the system; magnesium sulphate should always be given in these cases in

combination with the iodide, otherwise the metallic salt may be reabsorbed from the bowels.

Prescribing hints.—Potassium iodide is best administered freely diluted in water or milk, preferably an hour after food. When taken in this way the chances of iodism are less. While some patients suffer from iodism within a few hours after a relatively small dose, others bear quite large doses. Given soon after meals, it may cause gastric irritation from liberation of iodine, but taken half an hour before meals it is free from this effect. As they are incompatible with too many drugs, iodides should preferably be prescribed alone. They are incompatible with alkaloidal salts, and should not be prescribed with liquor strych. hydrochlor. which will throw down alkaloidal precipitate. Pot. iodide should not be used with calomel as it forms a highly irritating and toxic iodide of mercury. Acids for the most part decompose iodides setting free iodine. The same is true with hydrogen peroxide. Iodides precipitate heavy metals. When prescribed with ferric salts iodine is liberated, also when combined with spiritus ætheris nitrosi if acid. When combined with subnitrate of bismuth the mixture turns yellow from free iodine and from formation of iodide of bismuth.

CLASS C : Drugs used in Leishmaniasis

ANTIMONII ET POTASSII TARTRAS

(Antim. et Pot. Tart.)

Potassium Antimonyltartrate

Syn.—Antimonium Tartaratum; Tartar Emetic.

Source.—Obtained by the interaction of antimonious oxide and potassium acid tartrate. Contains not less than 99 p.c. potassium antimonyltartrate.

Characters.—Colourless, transparent crystals, or a white, granular powder; efflorescent; taste, sweet, no odour. *Soluble* in 17 parts of water, in 3 parts of boiling water, insoluble in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to 1 gr. or 0.002 to 0.008 grm. *Emetic.*— $\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. *Intravenously*— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

Note.—Solution for injection may be sterilised by heating in an autoclave, by tyndallisation, or by filtration.

ANTIMONII ET SODII TARTRAS

(Antim. et Sod. Tart.)

Sodium Antimonyltartrate

Source.—May be obtained by the interaction of antimonious oxide and sodium acid tartrate.

Characters.—Colourless and transparent, or whitish, scales or powder. No odour; taste, sweetish. Hygroscopic. *Soluble* in 1.5 parts of water, insoluble in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to 1 gr. or 0.002 to 0.008 grm. *Emetic.*— $\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. *Intravenously*— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

NON-OFFICIAL PREPARATIONS

1. **Vinum Antimoniale**—Tartarated antimony 4 grm., boiling water 4 mls., sherry *q.s.* to 1000 mls. *Dose*—10 to 30 ms. or 0.6 to 2 mls.

2 **Stibenyl**—Sodium acetyl-*p*-aminophenylstibinate—A brownish powder, soluble 1 in 10 parts of water. Can be given intramuscularly. Results have not been encouraging. *Dose*— $\frac{3}{4}$ to $1\frac{1}{2}$ gr. or 0.05 to 0.1 gm intravenously.

3 **Urea Stibamine**—A compound of urea and *p*-amino-phenylstibinic acid. Gives good results in the treatment of kala-azar with injections of 0.05 to 0.3 gm in 2 p.c. solution twice a week intravenously.

4 **Stibosan** *Syn.—Von Heyden*—It is a sodium salt of *m*-chloro-*p*-acetylaminophenyl stibinic acid. Useful in kala-azar. *Dose*—0.2 to 0.3 gm. Solutions should not be boiled and should be prepared fresh to make 1 to 2 p.c. solution. A stable compound and does not undergo any change when exposed to air.

5 **Neostibosan**. *Syn.—Von Heyden* 693 B—It is diethylamine-*p*-aminophenylstibinic acid. Can be given intramuscularly. 0.3 gm in distilled water to make 25 p.c. solution. Eight daily injections are given. The total quantity being 2.5 gm. *Dose*—0.05 to 0.2 gm. intravenously.

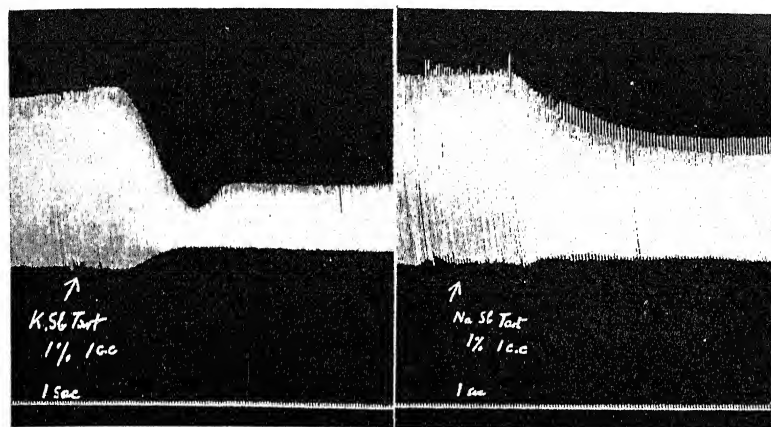
PHARMACOLOGY

Externally.—Salts of antimony are powerful irritants to the skin and form characteristic local lesions, first papular, then vesicular and lastly pustular. These rashes resemble small pox and are due to the formation of insoluble irritant precipitates at the orifices of the sweat glands by the acid perspiration. The pustules sometimes coalesce and form a big ulcer which on healing leaves an unsightly scar.

Internally.—In the stomach antimony has the same irritant action as observed on the skin, but the degree of irritation depends upon the amount used. In small doses it produces a sense of warmth and soreness, and in larger doses loss of appetite, nausea and increased secretion of gastro-intestinal mucus. In still larger doses (1 to 2 grs) it induces vomiting which is accompanied by depression, cold perspiration, hurried respiration and increased bronchial and salivary secretion. The vomiting is due to direct irritant action on the stomach, although it was once attributed to stimulation of the centre. The salts dissociate in the stomach and intestine and increase their peristaltic movement. But the antimony ion is slowly absorbed from the stomach, therefore the effects are entirely confined to the stomach, and since most of it is expelled out very little enters the intestine, unless a large quantity is used, or more passes into the intestine than is expelled out by the vomit. In toxic doses it is a powerful gastro-intestinal irritant like arsenic.

Heart and circulation.—From the beginning, even in small doses, antimony reduces the force and frequency of the cardiac beat which tends to become intermittent, and in large doses the heart becomes profoundly depressed with acceleration of the pulse-rate. The blood-pressure falls considerably (1) partly from the depressed condition of the heart, (2) partly from the relaxed state of the arterioles caused by the depression of some portion of the vaso-motor system, and (3) partly reflexly from the stomach (nausea). Hence, antimony is a powerful cardiac and circulatory

depressant. Antimony probably circulates in the blood in combination with proteins. It increases the number of leucocytes and is said to diminish the red blood-cells.



A

B

Fig. 25.—Perfusion of isolated Heart of Rabbit. A. Showing the effect of potassium antimony tartrate (1 c.c. of 1 p.c. solution). B. Effect of sodium antimony tartrate (1 c.c. of 1 p.c. solution). Note weakening and slowing of the heart, the effect is more marked with potassium salt.

Respiration.—Respiration is very much depressed after a brief stimulation. Inspiration becomes short, expiration prolonged, and finally respiratory movements become irregular. In fatal poisoning the lungs become congested. It increases the bronchial secretion and helps expectoration. This effect is chiefly reflex from gastric irritation.

Temperature is not much affected in health but is reduced in fevers, owing chiefly to diaphoresis, caused by (1) the depressed condition of the circulation, (2) dilatation of peripheral vessels, and (3) possibly to some extent from gastroenteritis.

Nervous system.—The cerebrum is depressed causing a feeling of languor, inaptitude for mental exertion, lowness of spirits and sleepiness. These effects are indirect through circulatory depression and disturbances of the gastrointestinal tract.

Metabolism.—Its effects on metabolism are much the same as those of phosphorus and arsenic. Continued long it causes fatty degeneration of many organs specially the liver. The glycogen may disappear from the liver, and there is increased elimination of nitrogen and deficient oxidation of tissues.

Micro-organisms.—Like arsenic, antimony in dilutions of 1 in 200,000 kills trypanosomes, and the trivalent antimony,

whether in organic or inorganic combinations, is more toxic than the pentavalent form. Antimony therefore has a specific action on trypanosome in much the same way as quinine on the malarial parasite. In fact Cushny has shown that in dilutions of 1 in 500,000 it has a destructive action on trypanosome in the blood. On the other hand Neguchi has pointed out that the highest dilution of tartar emetic lethal to cultures of leishmania is 1 in 100 *in vitro*, and that its action is not increased by contact with fresh animal tissue. In the body its concentration is not likely to be greater at any time than 1 in 10,000. Moreover pentavalent compounds are excreted more rapidly than trivalent derivatives. In fact Brahmachari has shown that 30 to 40 p.c. of urea stibamine is excreted within 24 hours after injection, whereas only 6 p.c. of tartrate is excreted in the same period. It is evident therefore that antimony by itself cannot cure kala-azar, and it has been suggested that either it forms a new compound with the tissues of the host which exerts a parasitocidal effect, or that it liberates from the tissues immune bodies which destroy the parasites.

Elimination.—Absorption of antimony is slow, the salts are excreted by the kidneys, bile, skin, mucous membranes of the bronchi, gastro-intestinal tract and mammary glands. A portion is stored up in the liver. A considerable amount is excreted by the intestine, a large portion is also thrown out by the kidneys.

Toleration.—Large doses given several times a day sometimes do not induce vomiting, thereby producing tolerance of the drug.

Acute toxic action is very much the same as that of arsenic. Pain and discomfort in the region of the stomach, headache, general weakness, profuse diarrhoea and jaundice are some of the symptoms. Albumin appears in the urine and the pulse becomes slow and weak. The *post mortem* appearances are not so marked as in arsenical poisoning.

Treatment.—Emetics or stomach-pump if vomiting is not free. *Tannin* is the chief antidote in any shape. Strong tea, coffee, gallic acid, astringent infusions, and demulcent drinks should be freely given. Stimulants, strychnine subcutaneously.

THERAPEUTICS

Externally.—As a *counter-irritant*, tartarated antimony ointment (5 p.c.) is used in cases of **kala-azar** of children who cannot be given intravenous injections. Application of 1 to 2 p.c. tartar emetic ointment has given good results in the treatment of **oriental sores**.

Internally. Gastro-intestinal tract.—As an *emetic*, tartar emetic is not suitable in cases of poisoning on account of its tardy action and the general prostration it induces, but is of great service in those cases of acute inflammatory affections of the respiratory tract, such as **croup** and **bronchitis** where

both emesis and vascular depression are needed. Formerly antimony was used largely in acute inflammatory fevers, but its use has now been given up. It is only used in cases of bronchial affections of children in combination with ipecacuanha tincture.

It is chiefly used in the treatment of several tropical diseases, such as leishmaniasis, trypanosomiasis, yaws and bilharziasis. It has also been used in malaria and filariasis, but the results have not been encouraging.

The treatment of leishmaniasis with antimony preparations constitutes one of the most important advances in chemotherapy. The best results are obtained when the treatment is commenced early. In fact 18 to 25 injections of tartar emetic or sodium antimonytartrate spread over two to three months will effect complete recovery. The routine method is to give these injections intravenously, commencing with 0.5 c.c. of a 2 p.c. solution and gradually increasing the dose by the same amount each week till a maximum of 4 to 5 c.c. is reached or until 2 to 3 grms. have been given. These injections can be given every 2 or 3 days as long as no toxic symptoms or any excessive reaction occur. Some prefer 1 p.c. solution. The solution can be sterilised by boiling. If any fluid escapes into the tissues around the vein there will be pain and inflammatory induration. According to Napier the maximum curative dose of tartrate is 4 grm. for every 100 pound of body weight. In practice however a maximum of 2.52 grm. in 30 injections is sufficient. The total amount required to produce complete cure possibly varies. For children or debilitated patients the initial dose should be 0.25 c.c. Children tolerate relatively larger doses than adults.

The success of the antimony treatment has led to the introduction of many preparations, but urea stibamine of Brahmachari, gives the best results, and cases resistant to tartrates or other preparations recover under its use. Although it is claimed by some workers that neostibosan is superior to many other preparations inasmuch as it effects a cure with eight daily injections, the results have not been so brilliant as anticipated, and it has no advantage except that it can be given intramuscularly. An adequate course of urea-stibamine in kala-azar for an adult is 1.5 to 2.5 grm., that for neostibosan is 4.0 to 5.0 grm. Urea-stibamine is therefore more potent.

Owing to the toxicity of the potassium salt, sodium tartrate of antimony is preferred by many in the treatment of bilharziasis. The routine method is to start with $\frac{1}{2}$ gr. dissolved in normal saline, and increase by $\frac{1}{2}$ gr. with each injection till a maximum of 2 gr. is reached. These injections are given on every alternate days. For children the initial dose is $\frac{1}{4}$ gr. Not more than 25 to 30 grs. are given during

the whole course. A trivalent antimony compound of pyrocatechin sodium disulphonate (**Fuadin**) has been used. The injections are given into the gluteal muscle. The usual dose is 15 c.c. of a 7 p.c. solution on the first day, 35 c.c. on the second day, and 5 c.c. on the third day, after which the same dose is given on alternate days till the fifteenth day. 5 c.c. contains 42.5 mg. of antimony. It has also given good results in *granuloma inguinale* when used in the same way as for bilharziasis.

The intravenous injection is contra-indicated where any pulmonary or gastro-intestinal complications are present. It should not also be given to patients suffering from chronic renal troubles or to those with feeble pulse and low blood pressure.

Toxic symptoms associated with intravenous injections.—As a rule no untoward symptoms are noticed in the majority of cases provided the treatment is commenced with small doses and gradually worked up to the maximum dose. A certain number of patients however show an intolerance to the drug, and untoward symptoms may appear even after very moderate doses. These symptoms may be classified as follows: (a) Gastro-intestinal symptoms. Severe fits of coughing and retching immediately after an injection is very common. These are less likely to occur if the injections are given on an empty stomach. Nausea and vomiting and sometimes acute diarrhoea may follow an injection. (b) A slight rise of temperature with or without rigor; this is of no significance unless excessive. (c) Cyanosis, rapid and irregular pulse. (d) Nervous symptoms. General depression when the treatment has been continued long, persistent headache and hemicrania. Rarely loss of consciousness and incontinence of urine and feces. (e) Pain on the shoulders and in the big joints. (f) Papular eruptions. (g) Symptoms suggestive of acute hepatitis with jaundice and recurrence of fever. (h) Anaphylactic-like syndrome. Generally occurs suddenly after the 6th or 7th injection. Face becomes puffy, urticarial rashes appear all over the body, and difficulty of breathing. In severe cases pulse becomes imperceptible and collapse sets in with stertorous breathing and unconsciousness. These symptoms disappear soon. Though alarming no deaths have been reported.

Appearance of any of these symptoms demands either reduction of the dose or stoppage of treatment.

Prescribing hints.—The use of antimony in the treatment of kala-azar is almost universal and the student should know its different methods of administration. In cases of children, or where its use is otherwise contra-indicated, tartar emetic ointment 5 p.c. or metallic antimony 5 to 10 p.c. in lanoline may be rubbed on the skin. Only small doses can be given by the mouth, and therefore in the treatment of protozoal diseases where stronger concentration is required this method is of no use. Intramuscular injections are very irritating and painful, producing severe inflammation. Although several preparations are now available which are claimed to have the advantage of not producing any local effect, the intravenous route is the only reliable method and should always be adopted. The injection is given with the patient lying down and this position should be maintained

for half an hour or longer if necessary. The injection should not be given unless the physician is certain of the needle being in the lumen of the vein. No food should be given for one hour after injection. Some patients are intolerant to even small doses of antimony.

Class D. Drugs used in Trypanosomiasis

These include pentavalent arsenic compounds, *viz.* Tryparsamide, Cocodylates (*see* page 494), Atoxyl, and Bayer 205, Moranyl.

TRYPARSAMIDE

Tryparsamide. (Tryparsamid.)

Source.—It is sodium N-phenylglycineamide-*p*-arsonate. Contains 25.1 to 25.5 p.c. of As in organic combination.

Characters.—A colourless, crystalline powder. Freely soluble in water.

B.P. Dose.—15 to 30 grs. or 1 to 2 grm., by subcutaneous, intramuscular or intravenous injection.

ACTION AND USES

Recently this preparation has been introduced for the treatment of trypanosomiasis. It causes disappearance of the human trypanosomes from the peripheral blood, specially the *Gambiense* infections. The usual dose is 0.3 to 3.0 grm. weekly in 10 p.c. solution intramuscularly or intravenously. The optimum dose is about 83 mg. per kilo of body weight. A total dosage of 24 grm. is, as a rule, necessary. During the second stage, with nervous symptoms, it produces marked improvement in the cell content of the cerebrospinal fluid with arrest of the symptoms, in doses of 3 to 5 grm. Only disadvantage is that it also causes transient dimness of vision. Van den Branden and his colleagues, in the Belgian Congo, advise a total of 20 to 40 grms. in early cases, and 50 to 100 grms. in chronic ones, in doses of 3 grms., and 0.5 to 2 grm. in children.

NON-OFFICIAL PREPARATIONS

Sodu Aminarsonas, B.P.C. Syn.—*Atoxyl*; *Soamin*.—Both soamin and atoxyl which are closely allied preparations were first tried in the treatment of sleeping sickness; the former more extensively than the latter. They both cause the trypanosomes to disappear from the peripheral blood for long periods. They were however found to be of little value in the sleeping stage as they do not penetrate the meninges.

A number of cases of recovery in the early stages have been recorded by different observers. The method of treatment is to give injections of either soamin or atoxyl in 10 p.c. solution once a week. The usual dose being 3 to 7 grs., commencing with 3 grs. and then working up to 7 grs. The only disadvantage is that it may cause dimness of vision and optic atrophy. The sight therefore requires to be tested during the course of treatment and any restriction in the field of vision necessitates either stoppage of the treatment or reduction of the dose. The routine method is either to give the injection every 5 or 6 days, or once a week for a month, or till 100 grs. have

been given and then to wait for one month before another course is given. This is continued for at least one year after all signs of the disease have disappeared (See also page 494).

Bayer 205. *Syn.—Germanin.*—A white amorphous powder, freely soluble in water and saline solution forming a neutral solution. Its composition is not known, probably belongs to the trypan red class of dyes. *Dose.*—0.6 to 1 grm. in 10 p.c. solution intravenously or intramuscularly every 2 to 6 days up to 5 injections.

Action and Uses.—Its action in this disease was established by giving injections of the drug to infected small animals, chiefly mice; and it has since been extensively used on human beings. The results were not very encouraging except in infections with *T. rhodesiense*. It is however more effective in early cases before the cerebrospinal fluid is infected. As a prophylactic it has been found rather effective giving protection for seven months. The total amount necessary to effect a cure is 10 grm., although the trypanosomes usually disappear after 5 grm. Its use is generally supplemented by the administration of tryparsamide, but it has been found that this increases the danger to sight of tryparsamide.

The drug is very expensive and produces toxic effects on the kidneys causing severe nephritis in some cases, which precludes its further use.

Moranyl. *Syn.—Fournneau 309.*—It is similar to Bayer 205, possibly of identical composition. Belongs to the class of trypanocidal dyes. Administered in 10 p.c. aqueous solution in doses up to 10 ml by subcutaneous or intravenous injection. This and Bayer 205 are inferior to arsenicals.

Class E: Drugs used in Amœbic infection

These include Ipecacuanha and its alkaloids (see page 309), Acetarsol, Chiniofonum, Carbarsone, Entero-vioform, Rivanol, Kurchi Bark

ACETA SOL

Acetarsol

Syn—Acetarsonic; "Stovarsol"

Source.—It is 3-acetyl-amino-4-hydroxyphenylarsonic acid. Contains 27.0 to 27.4 p.c. of As.

Characters.—A white, crystalline powder. Almost insoluble in cold water, soluble in dilute alkalis

B.P. Dose.—1 to 4 grs. or 0.06 to 0.25 grm.

Action and Uses

Acetarsol is therapeutically active when given by the mouth and has been used with some success in chronic amœbic dysentery, specially in the resisting cyst-passing cases. It is generally given by the mouth in 4 gr. doses twice a day after meals for ten days, which forms a course. The second course should be repeated after a rest of one week or better still two weeks. It is also given after a course of emetine to prevent relapse, but often fails to prevent this. It is used in lamblasis, treatment being given for one week. It has been tried in yaws, syphilis, trypanosomiasis and filarial infections but the results were not encouraging.

Its only disadvantage is that it has a tendency to induce dermatitis. A few cases of death are on record, therefore it should be used with caution.

CHINIOFONU**Chiniofon. (Chiniofon)**

Syn.—Pulvis Chiniofoni, "Quinoxyl"; "Yatren."

Source.—It is a mixture of approximately four parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part by weight of sodium bicarbonate. Contains 28.2 to 29.6 p.c. of I, and 18 to 22 p.c. of NaHCO₃.

Characters.—A light yellow powder; odourless; taste, bitter with a sweetish after-taste. Soluble with effervescence in about 25 parts of water; insoluble in alcohol (95 p.c.), in ether, and in chloroform.

Note.—Solutions are decomposed by boiling

B P Dose.—1 to 8 grs. or 0.06 to 0.5 gm. *By rectal injection*:—15 to 75 grs. or 1 to 5 grms

ACTION AND USES

Chiniofon is a relative of quinine and is bitter. Because of its iodine content it is an **antiseptic** and may be used for washing the bladder and vagina, and as a mouth wash in 2 to 3 p.c. solution.

Its chief use is in the treatment of **amœbiasis** in which condition it is administered both orally and also by rectal injection. As it is decomposed by the gastric juice it is given in enteric-coated pills in 4 gr. doses, three times a day for one week. Its use should be stopped for 8 or 10 days before it is again repeated. It has the disadvantage of producing diarrhoea. For rectal injection it is given in 2½ p.c. solution. About 200 c.c. being slowly thrown up the rectum by means of a funnel and tube and retained for 6 to 10 hours. This may be given several times a day at the beginning and then only once a day. It is not a specific but a valuable adjunct to other treatment, and is often given after a course of emetine injection or alternately with emetine-bismuth-iodide in amœbic dysentery. It has also been used in bacillary dysentery and lamblial cysts.

CARBARSONE (Not official).—4-carbaminol-phenyl arsonic acid. Contains 28.8 p.c. arsenic. It is extolled as a valuable remedy in amœbic dysentery and is non-toxic. It is administered by the mouth in 0.25 gm. or 3¼ gr. doses in capsules twice a day for 10 days. Although practically insoluble in water it may be dissolved in alkaline aqueous solutions and is readily absorbed after oral administration and can be given for prolonged period without eliciting any toxic effect. It does not produce any nausea or vomiting. In obstinate cases an enema of 2 gm. in 200 c.c. of warm 1 p.c. sodium bicarbonate solution is instilled into the rectum after a cleansing enema, and repeated every alternate night for five nights.

It is contra-indicated where the kidneys and the liver are damaged.

ENTERO-VIOFORM. (Not official).—Iodochlor-oxy-quinoline with sapamine. A greyish-yellow powder almost insoluble in water and sparingly soluble in alcohol. Contains 40 p.c. iodine.

Dose.—0.25 gm. or 3¼ gr. in tablets for ten days. The course being repeated after a week's rest. Total quantity being 15 gm.

It has been used in amœbiasis, bacillary dysentery and colitis with much success.

RIVANOL. (Not official). *Syn.*—Ethoxy-diamino-acridine lactate—A

yellow dye-stuff with powerful antiseptic action. Useful in human amebiasis, bacillary dysentery and acute and chronic enteritis of adults and children.

Dose.—0.025 grm. or $\frac{1}{4}$ gr. for adults; 0.008 grm. or $\frac{1}{8}$ gr. for children, 3 to 4 times a day. May also be used as enema, 10 to 20 oz. of 1 in 5000 to 1 in 3000 solution injected slowly.

CLASS F: Drugs used in Bacterial invasion

SULFONAMIDES



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
Syn.—Prontosil Album; Sulphonamide P; Streptocide; Col-sulanyde.

It is *p*-amino-benzene-sulphonamide. A white crystalline, odourless and almost tasteless powder. Sparingly soluble in water.

Dose.—8 to 30 grs. or 0.5 to 2 grm. in tablets.

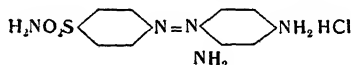
Owing to the introduction of proprietary names and because of their complicated chemical structure, much uncertainty exists regarding the nature of these compounds. All these compounds contain at least one benzene

ring  (C_6H_6), at least one amino group (NH_2), and at least one sulphonamide group (NH_2SO_2). By adding amino group to benzene ring—amino benzene, , i.e. aniline

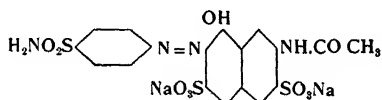
is formed. By attaching one sulphonamide group to the para position of amino benzene, para-aminobenzene-sulphonamide is formed, H_2NO_2S , shortly known as "Sulphanilamide", the mother substance of all the other derivatives. All other preparations are either modifications of sulphanilamide or compounds with a more complicated chemical structure. But all these compounds contain the three groups mentioned above.

OTHER NON-OFFICIAL DERIVATIVES

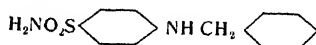
1. **Prontosil.** *Syn.*—*Prontosil Rubrum*—The hydrochloride of 4'-sulphamido-2,4-diaminoazobenzene. A red crystalline powder, soluble in 400 parts of water. **Dose.**—0.3 grm. in tablets. It is the original preparation.



2. **Prontosil Soluble.**—The disodium salt of sulphonamino-phenylazo-hydroxy-acetyl-amino-naphthalene-disulphonic acid. Soluble, 1 in 25 of water. **Dose.**—20 to 40 mls daily by *intramuscular injection*. Supplied in ampoules containing 5 and 10 mls of 25 and 5 p.c. solution for intramuscular injection. *By mouth* 3 to 6 tablets daily.

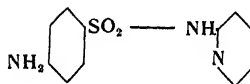


3 **Proseptasine Syn**—M and B 125—It is *p*-benzyl-aminobenzene-sulphonamide *Dose*—0.5 grm. in tablets *by mouth* Toxicity is negligible and larger doses can be given with safety



4 **Soluseptasine**.—It is disodium-*p*-benzene-sulphonamide. Said to be less toxic than sulphonamide *Dose*—5 to 20 mls of a 5 or 10 p.c. solution intravenously

5 **M and B 693**—2 (*p*-aminobenzene sulphonamido) pyridine *Dose*—0.5 grm in tablets or in ampoules for injection



PHARMACOLOGY

Till recently sterilisation of the blood stream against some bacterial infection was looked upon as an unattainable ideal, but the introduction of these compounds has altered the situation. It has been found that prontosil is effective against *Streptococcus haemolyticus*, and when given to a patient will differentiate between the protoplasm of the bacteria and that of man and thus attack the bacteria leaving the tissue of the human host uninjured.

It is decomposed in the body and it has been found that the activity of the drug lay in the sulphonamide part of the molecule and that sulphanilamide, weight for weight, is four times as active as prontosil. It has been found that the removal of the amino group from the para- position to the ortho- or meta- position destroyed the activity. Similar results also followed any attempt to substitute another radical in place of amino or the sulphamido-group. It follows therefore that to be effective three things are necessary, *viz.* (1) an amino-group attached to the benzene ring; (2) a sulphamido-group similarly attached; and (3) that these groups must be in the para position, one to another.

Administered by the mouth or given parenterally these compounds are readily absorbed, effectively penetrate all tissues including the cerebro-spinal fluid, and excreted by the kidneys. The maximum concentration of 10 mg. per 100 c.c. of blood is reached between three and four hours after the first dose of 1 grm. of M and B 693. The concentration remains between 8 to 10 mg. for 24 hours, after which it quickly drops to zero within the next 12 hours. The concentration in the cerebro-spinal fluid follows approximately parallel course; the maximum being half the concentration in the blood. This explains the necessity of giving repeated doses at short intervals in order to maintain a high concentration either in the blood or in the cerebro-spinal fluid.

How these drugs act is not clearly understood, although

different views have been put forward to explain their action in bacterial infections. These may be grouped as follows: (1) that they have a stimulating action on the specific and non-specific body defences; (2) that they neutralise toxic bacterial products; (3) that they act on the bacteria themselves, either as germicides (bacteriolysis), or in some other subtle fashion by interfering with invasive power or ability to multiply (bacteriostasis); and (4) some combination of two or more of the above. As a result of experiments, McIntosh and Whitby* have shown that these drugs do not stimulate leucocytic or phagocytic activity; that they do not affect the speed of production or the quality and quantity of specific immune bodies; that both in *vivo* and *vitro*, these drugs are not instantly active and that there is a quantitative relationship between the effective dose and the number of bacteria affected; that they are active on highly virulent organisms and those in the logarithmic phase of multiplication; they are inactive on "rough" organisms; and they are not simple germicides. They probably act by neutralisation of some metabolic function or enzymatic activity.

It has been suggested† that they do not help development of immunity, so that when the treatment is stopped there is just the possibility of a relapse. Moreover by stopping the activity of the infective organisms they may hinder formation of immunity in the body thus leaving the patient with a latent infection without the means to combat it.

These drugs are highly selective in their action since only certain bacteria are susceptible. It is therefore necessary that the nature of the infecting organisms should be known before administering this remedy. Even susceptible bacteria respond differently to the treatment; while some forms are inhibited by smaller doses for a short period, others require larger doses for longer period.

Excretion.—They are excreted with the urine in which they are detected within 45 minutes after administration by the mouth. Elimination is complete within 50 hours, but up to 60 p.c. is excreted within 24 hours. When given in adequate amounts, sulphanilamide is excreted in bactericidal concentration in the urine and prostatic secretion, and during excretion acts as direct poison to the infecting organisms in the urinary tract. Given in smaller doses it is not effective. The drug is more effective in alkaline urine. It has been found in the sweat and when given to pregnant animals in the amniotic fluid and the foetal blood. It distributes itself by simple diffusion.

Toxic action.—The most common symptom is cyanosis due to sulphæmoglobin and methæmoglobin being developed in the

**The Lancet*, Feb. 25, 1939.

†Cokkinis, *British Medical Journal*, Oct. 22, 1938.

blood. This is more common when the intestine contains sulphur or sulphates. Headache, nausea, vomiting, breathlessness, lassitude, general malaise and renal irritation are some of the common effects. Exfoliative dermatitis, photosensitisation of the skin as also skin rashes have been reported. Polyneuritis and optic neuritis. Agranulocytic anaemia is perhaps the most serious condition, it is fatal but rare. The benzene compounds are less toxic than the phenyl sulphonamides.

During administration of any of these compounds sulphur containing drugs, like magnesium sulphate, or foods, like eggs should be avoided as they are likely to cause sulphyloglobinæmia. It is also risky to use some of the coal-tar derivatives.

THERAPEUTICS

At first these drugs were used chiefly in the treatment of streptococcal infections, and the brilliant results which followed their use made the clinicians give these a trial in the treatment of other infections. In fact they are used in all infections with sulphonamide susceptible organisms, viz. *Streptococcus hæmolyticus*, *S. viridans*, *enterococcus*, *B. coli* and other coliform organisms, *gonococcus* and *meningococcus*, but not pneumococcus.

These derivatives have been used not only as a curative in **puerperal septicæmia** but also as a preventive before child-birth in patients who may have a septic focus. Similarly **prontosil** has yielded very good result in **erysipelas** and its administration is followed by rapid fall of temperature. It cuts short the spread of the disease and diminishes the mortality rate. They have been used with success in septic sore throat, otitis media, arthritis, etc. Recovery follows its use in **meningitis**, both streptococcal and meningococcal. In this condition it is used by intramuscular or intrathecal injections. The usual dose is 10 to 30 c.c. of 0.8 p.c. solution. These injections are continued until the cerebro-spinal fluid becomes sterile, when it should be given by the mouth in doses of 75 grs. (5 gm.) daily. They have been extensively used in gonorrhœa, cystitis and pyelitis due to *B. coli* and *B. typhosus*, and are of special value in urinary infection occurring during or after pregnancy. 0.2 gm. daily for six to eight days will clear up many cases of primary pyelitis or of pregnancy.

M. and B. 693 acts more favourably in the treatment of **pneumonia**. It reduces the temperature within 24 to 48 hours of giving the drug. Four tablets of 0.5 gm. are given as soon as the patient is seen, after four hours 2 tablets are given every four hours for 36 hours, to be followed by 1 tablet every four hours for another 36 hours. It has also been used with success in **gonorrhœa**. Six tablets (3 gm.) are given daily for four to five days, then four tablets a day for five days. For women four tablets (2 gm.) a day for 7 to 10 days followed by four tablets a day for five days during the menstrual period following cessation of treatment.

Prontosil soluble has been used in subtertian malaria with good results. Similarly cures from undulant fever and one case of recovery from actinomycosis have been reported.

Prescribing hints.—These preparations are as a rule given orally in doses of 75 grs. (5 grm.) a day. When the temperature comes down 45 grs. (3 grm.) daily are given. They may also be used by intramuscular or intravenous injection. Ampoules for injection are available, or 0.8 p.c. solution of sulphanilamide in physiological saline may be used. In bad infections, 2 to 4 grm. a day by the mouth or 20 mls of 2.5 p.c. solution intramuscularly every eight hours should be given. At first the dose is high and as the fever declines the dose should be reduced and continued for some days after the temperature comes down to normal.

Sulphanilamide is extremely diffusible and is rapidly excreted by the urine. It has the greatest bacteriostatic potency and a wide antibacterial range. In fact it arrests the growth of all sulphonamide-susceptible organisms with the exception of pneumococcus.

Prontosil Rubrum is used for oral administration in the form of tablets and Prontosil Soluble is used by injection. The antibacterial range and potency are less than sulphanilamide, but these are less toxic.

Proseptasine and Soluseptasine are the least toxic of all the sulphonamide compounds but they are less potent.

M. & B. 693 differs from sulphonamide in that one hydrogen of the SO_2NH_2 group has been replaced by a basic pyridine group. It has the bacteriostatic potency at least equal to that of sulphonamide and a wider range of antibacterial action since it acts on pneumococcus in addition to other organisms. It is a white or nearly white powder with a slightly bitter taste and is available in two forms, *viz.* compressed tablets of 0.5 grm. each for oral use, and ampoules containing the same amount for injection.

GROUP XVII

VOLATILE OILS

GENERAL ACTION OF VOLATILE OILS

Micro-organisms.—The volatile oils are protoplasmic poisons and act as **antiseptics**, both when used externally and also when taken internally. Some are more powerful in this respect and these belong chiefly to the turpentine group, and the empyreumatic oils are largely used as efficient antiseptics and disinfectants. This action depends upon their volatility and solubility in lipoids which enable them to enter the bacteria more easily. The only drawback is their insolubility in water.

Skin.—Applied to the unbroken skin they first stimulate then depress the local sensory nerves and produce irritation and itching followed by numbness. The irritation is accompanied by redness caused by dilatation of local blood vessels.

Volatile oils are therefore irritants, rubefacients and mild anæsthetics. Some of them; *e.g.* turpentine, rosemary, cajuput, mustard, etc., are powerful irritants and counter-irritants. Others again affect in a specific manner the nerve endings conveying the sensation of cold. To this class belong the stearoptenes, particularly menthol.

Alimentary canal.—The same irritant effect is observed in the mouth and stomach. Taken freely diluted, as in the form of aromatic waters, they stimulate the nerves of taste and produce a sensation of heat in the mouth and reflexly induce salivary and gastric secretions. In the stomach volatile oils are mild irritants and cause a sense of heat in the epigastrium and provoke appetite for food. They stimulate the gastric mucous membrane, increase its vascularity, accelerate the secretion, and give rise to eructation and expulsion of gas from relaxation of the sphincters. They are *stomachics*, *carminatives* and *mild antiseptics*. In concentrated form, or the more powerful ones, may give rise to gastro-enteritis with hiccough, vomiting and diarrhœa. The milder ones, *viz.* anise, dill, cinnamon, peppermint, etc., are largely used as *carminatives* and *flavouring agents*. Lower down in the intestine they increase their movements in small doses, while large doses decrease them. Clinically their use is followed by expulsion of gas and relief of colic, and they are largely used with purgatives. Some are *anthelmintics*, *e.g.* thymol, oils of chenopodium and turpentine.

Nervous system.—In ordinary therapeutic doses the effect on the nervous system is purely reflex from the mouth and the stomach. The vessels of the skin dilate and there is a feeling of warmth and relief of chill. The vaso-motor, accelerator and the respiratory centres are stimulated causing a rise of blood-pressure, acceleration of respiration, and a feeling of general well-being. The nervous system is affected directly only in large doses. The cerebrum is first stimulated and then depressed, but this differs in different preparations. Turpentine causes less excitement but more drowsiness, whereas camphor stimulates and produces cerebral excitement and convulsion.

Absorption and excretion.—Volatile oils are rapidly absorbed both from the stomach and intestine and are eliminated through the different secretions. They can be detected in the breath, urine and sweat, to which they impart their characteristic odour. They are excreted with the urine in combination with glycuronic acid and during excretion stimulate the renal cells and act as *diuretics*. Some, like sandal wood oil, copaiba, cubebs, buchu, etc., are powerful *genito-urinary antiseptics*. While excreted through the bronchial mucous membrane they stimulate the secretions of the bronchial glands and act as *expectorants* and *pulmonary antiseptics*. Some are extensively used as such.

but their value as antiseptic to the respiratory tract when used by the mouth is doubtful.

They circulate in the blood unchanged and cause leucocytosis, the polynuclear variety being mostly increased. This effect is due to their irritant action on the alimentary canal.

The volatile oils are classified as follows:—

Class A Turpentine Group

- 1 Oils: Oil of Turpentine, Oil of Pine (*Abietis*)
- 2 Resins and Oleoresins Colophony, Myrrh, Storax, Balsam of Peru, Balsam of Tolu

- 3 Empyrealumatic Oils: Tar, Coal Tar (*see* antiseptics), Oil of Cade

Class B Volatile Oils having Special Stimulating Effect on the Skin

- Oil of Eucalyptus, Oil of Cajuput, Oil of Rosemary, Oil of Mustard, Capsicum

Class C Genito-urinary Antiseptics and Diuretics

- Copaiba (*see* page 400), Oil of Sandal Wood (*see* page 401), Buchu (*see* page 402), Juniper (*see* page 395)

Class D Nauseants

- Asafetida, Valerian

Class E Calminatives and Flavouring Agents

- Cloves, Cardamoms, Caraway, Coriander, Anethi, Anise, Lemon, Fennel, Cinnamon, Nutmeg, Oil of Lavender, Peppermint, Ginger

CLASS A: Turpentine Group

LEU TE E INTHINÆ

Oil of Turpentine. (Ol. Terebinth.)

Syn.—Rectified oil of Turpentine

Source.—An oil distilled from the oleo-resin turpentine, obtained from various species of *Pinus*, and rectified.

Characters.—Limpid, colourless, liquid. Characteristic odour and a pungent, bitter taste. Sp. gr. 0.860 to 0.870. **Solubility.**—Soluble in 7 volumes of alcohol (90 p.c.), and in all proportions of ether, chloroform, and glacial acetic acid.

Composition.—Two isomeric bodies *d*- and *l*-pinene. Other constituents are resin acids, camphene and fenchene. *Dipentene* and polymeric *terpene* may also occur. Formic, acetic and camphoric acids and camphoric aldehyde.

B.P. Dose.—3 to 10 ms. or 0.2 to 0.6 mil, as an anthelmintic.—120 to 240 ms. or 8 to 16 mls.

OFFICIAL PREPARATIONS

- 1 Linimentum Terebinthinæ.—65 p.c.
- 2 Linimentum Terebinthinæ Aceticum.—44.5 p.c.

NON-OFFICIAL PREPARATIONS

1 *Terpin Hydras*, U.S.P. **Syn.**—*Terpin Hydrate*.—Colourless, lustrous crystals or a white powder. Efflorescent; action similar to turpentine, but less disagreeable and less toxic. Diminishes cough and expectoration. Used in *bronchitis*, *phthisis*, *hæmoptysis*. **Dose**, U.S.P.—4 grs. or 0.25 gm.

2 *Terpinol*, B.P.C.—A mixture of several terpenes. An agreeable aromatic liquid. In *chronic bronchitis* and *phthisis*. **Dose**—1½ ms. or 0.1 mil in pills or capsules.

PHARMACOLOGY

Externally.—When rubbed into the skin, it is a rubefacient, irritant, and counter-irritant, and later on a local

anæsthetic. In large amounts it is a vesicant. It is also a local antiseptic and disinfectant, and it is absorbed by the unbroken skin.

Internally. **Gastro-intestinal tract.**—The same action is observed when taken internally, *i.e.* it dilates the gastric vessels, and increases both the peristaltic movements and the secretion of gastric juice; at the same time it reflexly stimulates the heart, but on account of its sickening taste it is never used for this purpose as other volatile oils act equally well and are not so nasty. In the intestine it helps expulsion of flatus and is a strong carminative. In large doses it causes great vascular dilatation and purging, the stools containing large quantities of blood. In doses of 120 to 240 ms. it is an anthelmintic for tapeworm, but this treatment is too dangerous for adoption. As an enema (60 to 120 ms. in 4 pints of water with soft soap) it kills thread-worms.

Circulation.—The reflex effect on the heart has already been alluded to. It circulates as turpentine and causes a rise of blood-pressure from stimulation of the vaso-motor centre. In large doses the pressure falls from paralysis of the centre causing dilatation of the vessels and depression of the heart. It causes contraction of the small vessels, and since it causes clotting of the blood when locally applied it is a hæmostatic.

Respiration.—It irritates the bronchial mucous membrane, causing dilatation of the vessels, increase of the secretion, and stimulation of the muscular coats of the bronchi during excretion, and acts as an expectorant. If the secretion is purulent it is disinfected.

Nervous system —Large doses cause languor, hebetude, drowsiness and unsteadiness of gait. Toxic doses are followed by coma and paralysis of the sensory nerves with abolition of reflex action.

Kidneys.—Here its action is specially powerful. The renal vessels are dilated causing some diuresis. It appears in the urine in combination with glycuronic acid. Comparatively small doses may cause lumbar pain, scanty urine, albuminuria and hæmaturia, with all the symptoms of stranguery. After a large dose there may even be complete suppression of urine. The urine has a smell of violets.

Skin.—It is excreted by the skin and sometimes causes erythema.

THERAPEUTICS

Externally.—Turpentine *stupes* (flannels wrung out of very hot water and sprinkled with turpentine) are largely used in tympanitic distension of the abdomen, and to produce irritant or counter-irritant effects in various forms of acute and chronic inflammation, such as pleurisy and bronchitis. The liniments are valuable applications to painful areas, as in

neuralgia, myalgia, rheumatism and lumbago. Pure turpentine has been used as a parasiticide in the various forms of tinea. Turpentine may also be used for the cure of psoriasis in cases where chrysophanic acid causes too much irritation. On account of its property of constricting the vessels, turpentine is used as a hæmostatic to check the free oozing from many operations about the mouth, in which case its antiseptic properties are also of value. The vapour also checks the bleeding in hæmoptysis but the air of the patient's room must be saturated with it.

Internally. Gastro-intestinal tract.—In large doses (15 to 30 ms. emulsified every hour for a few hours) it is a hæmostatic in gastric ulcer and typhoid fever; whilst as an enema it relieves tympanitic distension of the abdomen.

Respiratory tract.—It is not much used as an inhalation, as oil of Siberian fir, terebene and eucalyptus oil are much more pleasant and less irritating. Given internally in small doses it is useful in chronic bronchitis.

It may be used as a diuretic, but since it irritates the kidneys, it should be used with caution. For the same reason its use as internal hæmostatic has been given up and is perhaps of little value.

Caution.—Turpentine must always be given cautiously on account of its liability to set up strangury, and *it should never be given at all to subjects of Bright's disease* as in cases of this kind it may cause fatal suppression of urine.

T E R E B E N U

Terebene. (Tereben.)

Source.—Obtained by steam-distilling the product of the limited action of sulphuric acid on oil of turpentine

Characters.—A colourless, or pale-yellow liquid, with a pleasant and characteristic odour, taste, aromatic, terebinthinate. Sp gr. 0.862 to 0.870. Almost *insoluble* in water, miscible with dehydrated alcohol

Composition.—A mixture of *dipterpene* and other hydrocarbons.

B P. Dose.—5 to 15 ms or 0.3 to 1 ml.

NON-OFFICIAL PREPARATION

1 Vapour Terebenæ, T.H.—Terebene 40 ms, Magnesii Carbonas Levis 20 grs, Water to 1 oz. A teaspoonful of this in a pint of water at 140°F. as an inhalation.

PHARMACOLOGY AND THERAPEUTICS

As an *expectorant*, it has been given with success in chronic bronchitis, winter cough and phthisis, especially when complicated with emphysema. It may be exhibited in various ways: (a) *Externally*, either as an inhalation in the form of the vapour, or 15 to 30 drops may be sprinkled on the cotton-wool of an antiseptic respirator, or it may be used as a spray; (b) *Internally*, as a mixture, either alone or combined with apomorphine and other expectorants; or five

drops may be taken a few times a day on a lump of sugar, or in capsules or thick syrup.

As an *antiseptic* and *sedative*, the vapour of terbene is useful in phthisis, in which disease it is usual to combine it with equal parts of phenol and thymol, or phenol and spirit of chloroform, and use 10 drops of this mixture for medicating the antiseptic respirator. Terebene acts on the mucous membrane of the urinary and gastro-intestinal tract in much the same way as turpentine.

Prescribing hints —Terebene must be given with caution to gouty patients, and to subjects of chronic kidney troubles, as it may increase the albuminuria in cases of this kind.

OLEU ABIETIS

(Ol. Abiet.)

Oil of Siberian Fir

Syn.—Oil of Pine, Pinol; Pumlinae.

Source —The oil distilled from the fresh leaves of *Abies sibirica*. Contains from 35 to 40 p. c. w/w of esters, calculated as bornyl acetate

Characters —Colourless or nearly so. Odour, pleasant, aromatic. Taste pungent. Sp. gr. 0.905 to 0.925

Composition —Contains bornyl acetate 45 p. c. *Pinene*, *camphene*, *dipentene* and *phellandrene*

NON-OFFICIAL PREPARATIONS

1. **Syrupus Pini**, B.P.C. —Pine Oil, Glycerin, Sucrose and Water. **Dose.**—30 to 60 ms. or 2 to 4 mls

2. **Linctus Pini**, Terpin et Heroin —Contains Heroin Hydrochlor. $\frac{1}{100}$ gr. and Terpin Hydrate $\frac{1}{4}$ gr. to each diachm. **Dose** —30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The action and uses of the oil of pine resemble that of the oil of turpentine, it is more pleasant, and is used in bronchitis, phthisis and emphysema. It may be inhaled from a handkerchief or better through an inhaler, or 60 ms. in one pint of boiling water, as a mild stimulant and antiseptic to the bronchial mucous membrane.

Internally.—Given internally it is excreted by the bronchial mucous membrane, stimulating and disinfecting its secretion, and is therefore useful in bronchitis and chronic wasting lung diseases. It may be taken on sugar or in the form of pastil.

COLOPHONIUM

Colophony. (Coloph.)

Syn.—Resina; Resina

Source.—The residue left after the distillation of the volatile oil from the oleo-resin of various species of *Pinus*

Characters —Translucent, light amber-coloured, compact, brittle glassy masses; fracture, shining; odour and taste, terebinthinate. **Solubility** —Freely in alcohol (90 p. c.), ether, benzene, carbon disulphide. Insoluble in water

Composition.—It is an anhydride of three isomeric *Abietic acids*, traces of a volatile oil, a *resene* and a bitter principle.

OFFICIAL PREPARATION

1. Emplastrum Colophonii *Syn.*—*Adhesive Plaster, Resin Plaster* —1 in 10

PHARMACOLOGY AND THERAPEUTICS

Externally.—Resin is an antiseptic and mild stimulant, and is therefore useful in indolent ulcers, wounds and sores. Basilicon ointment (colophony 26 p c, yellow beeswax, lard and olive oil) is an excellent application for this purpose, but is apt to prove too stimulating if used for any length of time. Its chief use now is in pharmacy, to impart consistency and adhesiveness to plasters and ointments.

MY HA

Myrrh. (Myrrh)

Syn IV—*Gandharasha, gandhabol, Bol Beng Bola, Sans.*

Source—An oleo-gum-resin obtained from the stem of *Commiphora molmol*, and probably other species of *commiphora*

Characters—In rounded or irregular tears, or masses of irregular tears, varying in size, reddish-brown or reddish-yellow externally, dry, covered with a fine powder. brittle, fractured surface irregular, somewhat translucent, brown, oily, with whitish marks. Odour, aromatic. Taste, aromatic, bitter, acid.

Composition—(1) *Gum* 57 to 61 p c (2) *A resin, myrrhin* 25 to 40 p c (3) *Myrrhol*, a volatile oil 25 to 8 p c (4) *A bitter principle*

B.P. Dose—5 to 15 grs or 0.3 to 1 grm.

OFFICIAL PREPARATION

1. Tinctura Myrrhæ.—1 in 5 *B.P. Dose*—30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY

Externally—Like other oleo-resins, locally, myrrh is a mild disinfectant, and stimulant to the ulcerated and mucous surfaces.

Internally. *Gastro-intestinal tract*—The same action is noticed in the mouth, throat, stomach and bowels. It promotes appetite, excites gastric secretion and peristalsis of the stomach and intestines, and is therefore a stomachic and carminative

Blood.—It increases the number of leucocytes, perhaps by stimulating lacteal activity. It stimulates phagocytosis.

Elimination.—It is excreted by the mucous membranes especially those of the respiratory and genito-urinary tracts, which it stimulates and disinfects; hence it is an expectorant, emmenagogue and uterine stimulant.

THERAPEUTICS

Internally.—Myrrh makes a good mouth-wash* for aphthous and ulcerated tongue, relaxed throat and spongy gums.

*℞

Tinct. myrrh	ms. 60
Glycerin	ms. 60
Aqua	ad oz 8

Its efficacy is increased if combined with borax, as in tinct myrrhæ et boracis. For receded and ulcerated gums, tinct myrrhæ and liquor iodi mitis make a superior preparation. For its stomachic and carminative properties, it is often used as an adjunct to purgatives. As a disinfecting expectorant, it is occasionally given in chronic bronchitis and bronchiectasis. For its emmenagogue property it is largely prescribed in amenorrhœa, in conjunction with aloes and iron. Some however doubt its emmenagogue action.

STYRAX

Storax. (Styr.)

Syn.—Styrac Preparatus

Source.—A balsam obtained from the wounded trunk of *Liquidambar orientalis*, purified by solution in alcohol, filtration, and evaporation of the solvent. Contains not less than 30 p.c. of the total balsamic acid

Characters.—A brown, viscous substance, transparent in thin layers, odour and taste, agreeable and balsamic. Entirely soluble in alcohol (90 p.c.), and ether.

Composition.—Consists of a resin mixed with an oily liquid. The resin consists of *storsinol* combined with *cinnamic acid*. The oily liquid consists of *styröl*, *ethyl cinnamate* and *styracem*.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Enters into —Tinct. Benzoini Composita

PHARMACOLOGY AND THERAPEUTICS

Storax resembles benzoin and the balsams of Peru and tolu in its action. It is rarely given internally except in the form of Friar's balsam. An ointment (1 in 4) is a parasiticide in scabies. Mixed with an equal part or twice its bulk of olive oil, it kills *Sarcoptes hominis* and pediculi, but albuminuria has been known to follow its application.

BALSAMUM PERUVIANUM

Balsam of Peru. (Bals. Peruv.)

Source.—A viscid balsam, exuded from the trunk of *Myroxylon Pereiræ*

Characters.—A viscid liquid dark-brown in bulk, reddish-brown, and transparent in thin layers. Free from stickiness or stringiness. Odour, agreeable, balsamic. Taste, acid. Solubility.—Insoluble in water, easily in chloroform, and 1 in 1 of alcohol (90 p.c.), but on addition of more alcohol the mixture becomes turbid.

Composition.—(1) A colourless, oily, aromatic liquid *cinnamern*, 53 to 66 p.c., and a dark resin 28 p.c. The liquid portion consists of benzyl cinnamate and benzoate of benzyl. (2) The resin consists of a resin alcohol with *cinnamic acid* and *benzoic acid*.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

PHARMACOLOGY AND THERAPEUTICS

Externally.—On account of the volatile oil it contains, balsam of Peru is an antiseptic and stimulant to the skin and abraded surfaces, and may be applied to wound, indolent ulcers, bed-sores, etc. An ointment (12½ p.c. in simple oint-

ment) cures sore nipples and cracked lips. It kills pediculi and the *acarus scabiei* and is more agreeable than sulphur.

Internally.—Like most volatile oils, it is a stimulant and carminative. During its elimination by the bronchial mucous membrane it stimulates and disinfects the bronchial secretion and is therefore used as an expectorant in chronic bronchitis.

ALSA U T LUTANU

Balsam of Tolu. (Bals. Tolu.)

Source.—Obtained from incisions in the trunk of *Myroxylon Toluifera*. Contains 19 to 25 p.c. of the free balsamic acids, and 35 to 50 p.c. of total balsamic acids.

Characters.—A soft, tenacious brownish-yellow or brown solid when imported, hardens on keeping, brittle in cold weather, transparent in thin films. Odour, aromatic, vanilla-like. Taste, aromatic. *Solubility.*—In alcohol (90 p.c.).

Composition.—(1) *Benzoic acid* 8 p.c. (2) *Cinnamic acid* 12 to 15 p.c. (3) A resin 80 p.c. yielding *tolu-resinotannol* (4) 7.5 p.c. of an oily liquid consisting of *Benzyl cinnamate* and *Benzyl benzoate*. (5) 15 to 30 p.c. of a very fragrant volatile oil.

B.P. Dose.—5 to 15 grs or 0.3 to 1 grm.

Enters into.—Tinct. Benzoin Co

OFFICIAL PREPARATIONS

- 1 Syrupus Tolutanus —25 p.c. B.P. Dose —30 to 120 ms. or 2 to 8 mls
- 2 Tinctura Tolutana —10 p.c. B.P. Dose —30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Its action resembles those of balsam of Peru. The syrup is used as a flavouring vehicle for cough mixture. The tincture is a feeble expectorant.

LEU CA INU

Oil of Cade. (Ol. Cadin)

Syn.—Juniper Tar Oil

Source.—An oily liquid, obtained by the destructive distillation of the woody portions of *Juniperus Oxycedrus*

Characters.—A dark reddish-brown, or nearly black, viscid oily liquid. Odour, empyreumatic. Taste, aromatic, bitter, acrid. Sp. gr. 0.975-1.010 *Solubility.*—Freely in chloroform and ether, partially in cold, almost wholly in hot alcohol (90 p.c.), and slightly in water

Composition.—*Cadinene*, $C_{15}H_{24}$, a sesquiterpene.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The oil of cade resembles tar in its action, but has a more pleasant odour. It may be used in chronic inveterate eczema, psoriasis and other skin diseases attended with itching. It is applied in the form of an ointment (25 p.c.) combined with yellow beeswax and yellow soft paraffin, or simple cerate, or in a liquid form (oil of cade 1, soft soap 5, alcohol (90 p.c.) 4).

CLASS B: Volatile Oils having Special Stimulating
Effect on the Skin

OLEU EUCALYPTI

Oil of Eucalyptus (Ol. Eucalyp)

Source—The oil distilled from the fresh leaves from various species of *Eucalyptus*, and rectified. Contains not less than 70 p.c. of *Cineole*

Characters—Colourless or pale yellow Odour, aromatic, camphoraceous. Taste, pungent, leaving a sensation of coldness in the mouth Sp gr 0.910 to 0.930.

Composition—(1) *Eucalyptol* (cineole), a volatile oil. (2) A *terpene* called *phellandrene*, *butyric* and *valerianic aldehydes*

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil

EUCALYPT L

Eucalyptol. (Eucalyp.)

Syn.—Cineole

Source—It is the anhydride of 1.8-terpin or menthan-1.8-diol, and may be obtained from oil of eucalyptus. Contains not less than 97.5 p.c. w/w of cineole, $C_{10}H_{18}O$.

Characters.—A colourless liquid, odour, characteristic, aromatic and camphoraceous; taste, pungent and cooling. Sp gr 0.923 to 0.930.

B.P. Dose—1 to 3 ms. or 0.06 to 0.2 mil.

NON-OFFICIAL PREPARATIONS

1. *Nebula Eucalyptolis Composita*, B.P.C.—Eucalyptol 80 mil, camphor and menthol, each 20 g \ddot{m} , thymol 1 g \ddot{m} , light liquid paraffin, *q s* 1000 mil

2. *Vapour Eucalypti Co.*, B.P.C. *Syn*—*Anti-catarrhal Salts*—Phenol and oil of eucalyptus each, 16.50, oil of Siberian fir 8.25, strong solution of iodine 8.25, camphor 16.50, ammoniated alcohol 34.00.

PHARMACOLOGY

Externally.—Oil of eucalyptus or eucalyptol is a powerful antiseptic and disinfectant. The old oil is more antiseptic than the new because it is more ozonised. Rubbed into the skin it is less irritant than other volatile oils, but if evaporation be prevented it causes rubefaction and vesication. It is destructive to the lower forms of life

Internally. Gastro-intestinal canal.—In small doses it increases the salivary and gastric secretions, and thus acts as a stomachic. In large doses it produces gastro-intestinal irritation with symptoms of vomiting, diarrhœa and colic

Circulation.—Like quinine, it stops the amœboid movements and diapedesis of the white blood-corpuscles and contracts the engorged spleen. It possesses also mild anti-periodic and antipyretic properties. In small doses it stimulates the heart and raises the blood-pressure reflexly through the stomach; and in excessively large doses the heart becomes weak and the blood-pressure and temperature fall.

Respiration is slightly stimulated by small doses, and is slowed by large ones. Death occurs from respiratory paralysis.

Nervous system.—Large doses depress the action of the brain, the medulla and the cord, thereby paralysing the reflex action.

Elimination.—Like most of the volatile oils, eucalyptol is eliminated by the kidneys, the skin, and the respiratory and the genito-urinary mucous membranes, all of which it stimulates in the course of its passage. Hence it is a diuretic, diaphoretic, a stimulating expectorant, and a disinfecting stimulant to the genito-urinary tract. Like oil of turpentine it causes renal congestion and imparts to the urine an odour like that of violets.

THERAPEUTICS

Externally.—Oil of eucalyptus, though a valuable antiseptic, cannot be freely used on account of its local irritant property and cost. However, the ointment may be used for foul ulcers and wounds. The gauze, lint and wool are often used as antiseptic surgical dressings. Alone or mixed with mustard oil or olive oil it may be rubbed into the skin in chronic rheumatism and myalgia. The vapour (60 drops of eucalyptol in hot water) has been used as an inhalation in pulmonary gangrene, phthisis, chronic or foul bronchitis, etc. Many treat patients suffering from exanthemata, whooping cough and diphtheria by enveloping them in an atmosphere of eucalyptus vapour.

Internally.—To correct fetor of the expectoration or to cut short an attack of coryza, influenza or catarrh, it may be used with benefit (5 to 10 drops of eucalyptol on sugar). It is used in malaria but it is far inferior to quinine. As a stomachic and carminative it has occasionally been prescribed in dyspepsia.

L U CAJUPUTI

Oil of Cajuput. (Ol. Cajuput.)

Syn I V.—*Kayaputir tel*, Beng, *Kayaputi ke tel*, Hind, Bom

Source.—Distilled from the fresh leaves and twigs of *Melaleuca Leucadendron*, and other species of *Melaleuca*, and rectified by steam distillation.

Characters—Colourless or yellow liquid, odour, agreeable and camphoraceous, taste, aromatic, bitter and camphoraceous Sp. gr. 0.915 to 0.926. Colourless when rectified. **Solubility**—In 2 volumes of alcohol (80 p c)

Composition—(1) *Cineole* $C_{10}H_{18}O$, 50 to 60 p c (2) A crystalline *terpeneol*; *l-pmene*, several *aldehydes*

B.P. Dose—1 to 3 ms or 0.06 to 0.2 ml

OFFICIAL PREPARATION

- 1 **Spiritus Cajuputi**—1 in 10. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—It is used as a gentle counter-irritant on the chest in bronchitis, pneumonia, etc.; and over painful and

chronically inflamed joints. It may be mixed with mustard oil or other stimulating and anodyne liniments.

Internally—It is a powerful diffusible stimulant, carminative and antispasmodic. It is an excellent remedy for flatulent colic or intestinal spasm, sometimes relieving the pain by a single dose of 20 ms of the alcoholic solution. For repeated administration an excellent combination is oil of cajuput 2 ms, thymol and menthol each $\frac{1}{2}$ gr., chloroform pure 1 m., oleo-resin of capsicum 1 gr., in keratin-coated capsules.

Prescribing hints.—It may be given on sugar, in sherry, or in the form of an emulsion or pill.

OLEU ROS ARINI

Oil of Rosemary. (Ol. Rosmarin.)

Source—The oil distilled from the flowering plant of *Rosmarinus officinalis*. Contains not less than 2 p.c. w/w of esters, calculated as *bornyl acetate*, and not less than 9 p.c. w/w free alcohols, calculated as *borneol*.

Characters—Colourless or pale yellow, odour of rosemary, taste, warm, camphoraceous. Sp. gr. 0.900 to 0.919. *Solubility*—1 m. l. of alcohol (90 p.c.)

Composition.—(1) *Borneol*, 8 to 16 p.c. (2) *Bornyl acetate* and other esters, about 2 to 5 p.c. Camphor, cineole, pinene and camphene.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

PHARMACOLOGY AND THERAPEUTICS

Externally.—It is a stimulant and rubefacient to the skin, and is commonly used in the form of hair oil or hair wash to promote the growth of hair on the scalp in baldness. It is combined with liniments for its odour. Whitla recommends the following as a valuable application in baldness*. It is rarely used internally.

OLEUM SINAPIS VOLATILE

Volatile Oil of Mustard. (Not official)

Source.—The volatile oil distilled from *black* mustard seeds, deprived of most of their fixed oil and macerated in water for several hours.

Characters—Colourless or pale yellow, intensely pungent and irritant with an acrid taste.

Composition.—Seeds contain glucoside *sinigrin* and an enzyme *myrosin*. In presence of water sinigrin is hydrolysed by the enzyme forming *allyl isothiocyanate*, C_6H_5NCS , also contains *allyl cyanide*, *carbon disulphide* and traces of *isomeric allyl thiocyanate*.

NON-OFFICIAL PREPARATIONS

1 **Linimentum Sinapis, B.P.C.**—Volatile oil of mustard 5 mil., camphor 55 grm., castor oil 125 mil., alcohol (90 p.c.) to 1000 mil.

*R

Liq. epispast.	ms. 120
Ol. rosmarin	ms. 240
Ol. amygdal.	oz. $1\frac{1}{2}$
Sp. camph.	oz. 2
Glycer acid boric.	oz. 1
Ol. rosæ.	ms. 8
Tinct. jaborand.	oz. 1

2 **Thiosinamina** *Syn*—*Rhodallin*, *Allylthiourea*—Colourless crystals of slight garlic odour and bitter taste. Formed by warming oil of mustard with alcoholic solution of ammonia. Soluble in water, alcohol and ether. 15 to 20 p.c. solution used hypodermically for *lupus*. *Dose*— $\frac{1}{2}$ gr. to $1\frac{1}{2}$ grs. or 0.03 to 0.1 gm.

3. **Injectio Thiosinaminæ et Sodii Salicylatis**.—Consists of thiosinamin 10 p.c. and sodium salicylate 5 p.c. *Dose*—8 to 15 ms. or 0.5 to 1 mil every two or three days, 1 c.c. contains approximately 1 gr. of thiosinamin and $1\frac{1}{2}$ gr. of sodium salicylate.

PHARMACOLOGY

Externally.—Mustard is a powerful local irritant, rubefacient and vesicant. When it is first applied there is a sensation of warmth followed by severe burning pain, due to the irritant action of the mustard on the sensory nerves and increased local blood-supply. This irritation is quickly followed by paralysis, as a result of which there is loss of sensibility and a diminution both of the pain produced by the mustard and of any that may have existed previously. Mustard is also a counter-irritant. The excitation of the sensory nerves may reflexly stimulate the cardiac and respiratory centres.

Internally **Gastro-intestinal tract**.—Taken in small doses as a *condiment*, mustard causes a sense of warmth in the stomach, stimulates the secretion of gastric juice and peristalsis, and therefore sharpens the appetite. In large doses, it acts as a prompt and efficient *emetic* without causing the usual depression.

THERAPEUTICS

Externally.—A linseed poultice, having a little mustard (1 in 16) dusted over it, is a very common and efficacious irritant and counter-irritant in rheumatism, pleurisy, pneumonia, and bronchitis.

A mustard plaster will soothe pain in gastralgia, colic, neuralgia, lumbago, etc. When put over the epigastrium it often relieves vomiting, and when applied to the calves of the legs, it is a reflex stimulant in cases of syncope, asphyxia and coma.

Severe headache, common colds, and febrile conditions specially in children, are greatly relieved by a hot pediluvium or foot-bath, whilst infantile convulsions may be checked by immersion of the whole of the patient's body in a mustard bath containing one tablespoonful of mustard to each gallon of water.

A mustard sitz bath (*i.e.* hip bath) may be taken at the time of the period to induce menstruation when it has been suppressed by a chill.

Internally.—As an *emetic*, mustard is specially valuable in narcotic poisoning on account of its reflex stimulant effects. Give one to four teaspoonfuls in a tumbler of warm water.

Injections of thiosinamin soften the scar tissue and have been advocated for prolonged periods in *stricture of the œsophagus*, *stenosis of pylorus*, *perigastric adhesions*, *hour glass contraction of the stomach*, *urethral stricture*, *middle ear deafness*, *Dupuytren's contraction*, etc., and in certain sclerotic spinal cord diseases. Some observers report no improvement as the result of numerous injections long continued, and the injections have, in some cases, been followed by the onset of purpura hæmorrhagica.

CAPSIUM

Capsicum. (Capsic.)

Syn.—Small Chillies, Guinea Pepper, Pod Pepper, *Capsici Fructus*

Syn. IV—*Dham Lanka*, Beng *Gach Marich*, Hind

Source—The dried ripe fruit of *Capsicum minimum*

Characters—Dull orange-red oblong, conical, obtuse two-celled fruits about 12 to 20 mm. long, up to 7 mm. wide, sometimes attached to a 5 toothed inferior calyx and a straight, slender pedicel. Pericarp somewhat shrivelled,

glabrous, translucent, and leathery, containing 10 to 20 flat, reniform seeds, 3 to 4 mm long. Odour, characteristic, taste, intensely pungent.

Composition—(1) *Capsaicin* or *Capsacutin* (0.14 p.c.) a crystalline colourless pungent principle. (2) A liquid alkaloid. (3) An oleo-resin. (4) A fixed oil and red colouring matter.

B.P. Dose— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

OFFICIAL PREPARATIONS

- 1 *Tinctura Capsici*—5 p.c. B.P. Dose—5 to 15 ms. or 0.3 to 1 ml.
- 2 *Unguentum Capsici* *Syn*—*Chillie Paste*—25 p.c. approximately.

PHARMACOLOGY

Externally.—It is a powerful irritant, rubefacient and therefore counter-irritant.

Internally. **Alimentary canal**—In small doses it stimulates the secretion of saliva and gastric juice and increases peristaltic movements. It is therefore a sialagogue, stomachic and carminative. In large doses it is a gastro-intestinal irritant.

It is a cardiac and vascular stimulant, feeble narcotic, diuretic and aphrodisiac.

THERAPEUTICS

Externally.—Like cantharidin, capsicum may be used to promote the growth of hair. *Emplastrum capsici* (1 in 50 with resin plaster), or the ointment may be applied in rheumatism, lumbago or torticollis. A piece of lint soaked in an infusion of the pods and covered with oiled silk may be used for the same purpose.

Internally.—It is chiefly used as a condiment in India. The tincture mixed with tannic acid (1 dr. of each in water 10 ozs.) makes a useful gargle in relaxed throat, simple tonsillitis and chronic pharyngitis. It is an excellent remedy in atonic and flatulent dyspepsia and dipsomania.* In the last, it not only checks the craving but stimulates and tones the gastric functions. The same prescription will generally be found to be an effective “pick me up”.

CLASS D: Nauseants

ASAFOETIDA

Asafetida. (Asafœt.)

Syn I V.—*Hing*, Beng *Hingra*, Hind, Bom

Source.—An oleo-gum-resin obtained by incision from the living rhizome and root of *Ferula foetida*, or other species of *Ferula*.

Characters—In rounded or flattened masses, agglutinated, from 12 to 25 mm in diameter, or dull yellow tears, darkening on keeping. Internally yellow-

*R

Tinct capsic.	ms.	10
Sp. ammon aromat	ms.	30
Sod biom.	gr.	10
Tinct. cinchon. co.	ms.	20
Aq. chlorof	ad oz.	1

532 PHARMACOLOGY AND THERAPEUTICS

ish, translucent, or milky-white, opaque. Odour, strong, persistent alliaceous. Taste, bitter, acrid, alliacious. When triturated with water forms a white emulsion.

Composition.—(1) *Volatile oil*, 6 to 17 p.c. containing essential oil of garlic, allyl polysulphide which gives it its peculiar odour. (2) A resin, *asaresinotannol*, 65 p.c. (3) *Gum*, 25 p.c.

B.P. Dose—5 to 15 grs. or 0.3 to 1 grm.

OFFICIAL PREPARATIONS

1. *Pilula Aloes et Asafoetidae*—30 p.c. **B.P. Dose**—4 to 8 grs. or 0.25 to 0.5 grm.
2. *Tinctura Asafoetidae*.—20 p.c. **B.P. Dose**.—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY

Internally. Gastro-intestinal canal.—Like aromatic oils and resins, it is a stimulant, carminative and antispasmodic expelling flatus and relieving spasm; but its unpleasant nauseous taste is a drawback to its use.

Lungs—It increases and disinfects bronchial secretion during its elimination. Hence it is a disinfectant expectorant.

Nervous system.—It reflexly stimulates the nervous system through the mouth and stomach.

Excretion.—By the bronchial secretion and urine.

THERAPEUTICS

Externally.—A thick emulsion prepared by triturating with water is often applied with benefit to the abdomen of infants in tympanites.

Internally.—It is rarely used now except as a sedative in hysteria and allied conditions and as a carminative in flatulence. In the latter condition it may be given as an enema (30 grs. rubbed up with water 4 ozs.). Cases of malingering may be cured sometimes by giving effervescing draughts containing a few minims of tinctures of asafoetida and valerian, three or four times a day.

It is best given in pills, capsules or tincture.

VALERIANA

Valerian (Valerian.)

Syn.—*Valerianæ Rhizoma*.

Source—The dried rhizome and roots of *Valeriana officinalis*, collected in the autumn.

Characters—*Rhizome* 2 to 4 cm. long, entire or longitudinally divided, yellowish-brown externally, whitish internally, fracture, short, and horny. cortex parenchymatous with starch grains; endodermal cells contain volatile oil. *Roots*. Numerous, slender, brittle, 2 to 10 cm. long, piliferous layer papillose, with root hairs; exodermis of large cells containing volatile oil. Odour, strong and characteristic, taste, sweetish, camphoraceous and slightly bitter.

Composition—Its chief constituent is a volatile oil, 1 p.c., consisting of *bornyl isovalerate*, *formate*, *butyrate*, and *acetate*, united with *l-pinene*, *l-camphene*, and *l-limonene*. The oil has no odour when freshly distilled but on exposure to air develops the characteristic odour.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

OFFICIAL PREPARATION

1. *Tinctura Valerianæ Ammoniata*.—20 p c B P Dose —30 to 60 ms. or 2 to 4 mils.

ZINCI VALERIANAS

Zinc Valerianate. (*Not official*)

Characters—In white, pearly, tabular crystals with a characteristic disagreeable odour and metallic taste. *Soluble* in hot water and alcohol (90 p c)

Dose—1 to 3 grs or 0.06 to 0.2 gm

PHARMACOLOGY AND THERAPEUTICS

Small doses of valerian, like other volatile oils, produce a sensation of warmth in the epigastrium, a quickened pulse, and some mental excitement. There are considerable differences of opinion as to the manner in which valerian produces its effects

The ammoniated tincture is useful as a carminative in flatulence; and as a reflex stimulant in faintness and palpitation, but the essential oil (2 to 5 ms) suspended in mucilage with cinnamon water is better.

It is largely used in hypochondriasis, hysteria, nervous headache and other neurotic conditions in the form of the tincture with bromides, or as an extract (1 to 5 grs) with camphor monobromata for its supposed stimulating action on the psychical functions and the circulation. Its effects are however purely mental produced by its unpleasant taste and odour. In fact most of these cases yield to suggestion and use of charms, etc

CLASS E: Carminatives and Flavouring Agents

CARYOPHYLLUM

Clove. (Caryoph.)

Syn IV—*Lobanga*, Beng. *Long*, Hind

Source—The dried flower-buds of *Eugenia aromatica*.

Characters.—10 to 17.5 mm long, bright reddish-brown, wrinkled, subcylindrical, calyx, which tapers below is surrounded by four thick, rigid, patent teeth between which are four pale imbricated petals enclosing stamens and a single style. Odour, strong fragrant, spicy Taste, very pungent, aromatic.

Composition—(1) *Volatile Oil* (off) 15 to 20 p.c (2) *Caryophyllin*, a crystalline body. (3) *Gallo-tannic acid* (4) resin, etc.

B P Dose.—2 to 5 grs or 0.12 to 0.3 gm.

Enters into.—*Pulv. Cretæ Arom.*

OFFICIAL PREPARATIONS

1. *Infusum Caryophylli Concentratum* —B P. Dose —30 to 60 ms. or 2 to 4 mils.
2. *Infusum Caryophylli Recens* —2.5 p.c. Should be used within twelve hours of its preparation. B.P Dose — $\frac{1}{2}$ to 1 oz. or 15 to 30 mils.

OLEU CARYOPHYLLI

Oil of Clove. (Ol. Caryoph.)

Source.—The oil distilled from Clove Contains between 85 to 90 p c. v/v of *eugenol*, $C_{10}H_{12}O_2$.

Characters—Colourless or pale yellow liquid when recent, becoming reddish-brown gradually. Sp. gr. 1.047 to 1.060. Heavier than water.

- Composition**—(1) *Eugenol*, chemically resembling phenol (2) *Aceteugenol*.
 (3) *Caryophyllene*, a sesquiterpene, fufural and methyl-amyli-ketone
B P. Dose—1 to 3 ms or 0.06 to 0.2 ml.

PHARMACOLOGY

Externally.—Oil of clove acts like camphor, and is therefore a local stimulant, rubefacient, counter-irritant and anæsthetic. It is also a parasiticide and antiseptic.

Internally. Alimentary canal.—The local action of the oil of clove on the mouth is the same as on the skin. It reflexly stimulates the secretion of saliva and mucus and sharpens the appetite by stimulating the nerves of taste and smell. Simultaneously, the gastric circulation is reflexly excited with increased flow of the gastric juice.

It directly stimulates the stomach, thereby increasing the secretion of the gastric juice and the peristaltic movements. It is therefore a stomachic tonic and carminative. Like camphor or alcohol, it also reflexly stimulates the heart. It is an intestinal antispasmodic.

Elimination.—Like other volatile oils it is eliminated by the kidneys, genito-urinary tract, skin, bronchial mucous membrane, liver, and probably the bowels. In its passage it stimulates and disinfects their secretions but not so powerfully as turpentine or many other volatile oils.

THERAPEUTICS

Externally.—On account of its high price oil of clove cannot be freely used. Occasionally it is applied as an *anodyne* in superficial neuralgias. Very often it is employed for flavouring hair-oils and liniments. It is also very useful for *keeping off mosquitoes* for which purpose a little should be rubbed on to the hands and feet immediately before retiring to rest. In this way it acts as a prophylactic against malaria.

Internally.—Clove is generally used in cookery to improve flavour, and with aromatic bitters, to stimulate appetite and digestion. The oil relieves toothache when put into the cavity of the decayed tooth. It is an excellent remedy for intestinal colic and flatulence. It may be combined with purgatives to prevent griping.

Prescribing hints.—The oil is best given on a lump of sugar or triturated with sugar as *elæosacchara*, or suspended in mucilage.

CAR A UM

Cardamom. (Cardam.)

Syn—Cardamomi Semina. **Syn. IV**—*Elachi*, Beng.

Source—The dried ripe or nearly ripe seeds of *Elettaria Cardamomum*. The seeds should be kept in their pericarps and separated when required for use.

Composition.—(1) A volatile oil (2) A fixed oil. The pericarp is inactive medicinally.

B P. Dose—10 to 30 grs or 0.6 to 2 gm.

OFFICIAL PREPARATION

- 1 Tinctura Cardamomi Composita.—B.P. Dose —30 to 60 ms. or 2 to 4 mls

PHARMACOLOGY AND THERAPEUTICS

Internally.—Cardamom seeds are stimulant, stomachic and carminative and are therefore useful in flatulence and for correcting the griping property of purgatives. The tincture is a colouring and flavouring agent.

CARUM

Caraway

Syn.—Caraway Fructus. Syn. I.V.—*Jina*, Hind.

Source.—The dried fruit of *Carum Carvi*

Characters.—Mericarps separate, each 7 mm. long, 2 mm broad, brown, with pale ridges, slightly curved, tapering, glabrous. Odour, aromatic. Taste, aromatic, agreeable

Composition.—(1) The volatile oil (off)

B.P. Dose.—10 to 30 grs or 0.6 to 2 gm

OLEUM CARI

Oil of Caraway. (Ol. Cari)

Source.—The oil distilled from Caraway and rectified. Contains 53 to 63 p.c. w/w of *carvone*, $C_{10}H_{16}O$.

Characters.—Colourless or pale yellow liquid having the odour and taste of the fruit. Sp gr. 0.910 to 0.920

Composition.—(1) *Carvone* an unsaturated ketone. (2) Terpene or *d*-limonene, also called *Carvone*. (3) *Cymene*

B.P. Dose.—1 to 3 ms or 0.06 to 0.2 ml.

Uses.—The same as those of anethi.

CORIANDRUM

Coriander. (Coriand.)

Syn.—Coriandri Fructus. Syn. I.V.—*Dhana*, Beng, Hind.

Source.—The dried ripe fruit of *Coriandrum sativum*.

Characters.—Nearly globular, 3 mm. in diameter, uniform, brownish-yellow glabrous. Two mericarps closely united, and crowned by calyx teeth and stylopod. Odour, aromatic, especially when bruised. Taste, agreeable.

Composition.—The Volatile Oil (off)

B.P. Dose.—5 to 15 grs or 0.3 to 1 gm.

OLEUM CORIAN RI

Oil of Coriander. (Ol. Coriand.)

Source and characters.—A colourless or pale-yellow oil obtained by distilling Coriander. Solubility.—1 in 3 of alcohol (70 p.c.) Sp gr. 0.870 to 0.884.

Composition.—(1) *Coriandrol*—the dextro-isomeride of linalol (2) *d*-pinene, *l*-pinene, geraniol and borneol.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 ml

PHARMACOLOGY AND THERAPEUTICS

The action and uses of coriander fruit resemble more or less those of dill and anise fruits. The oil is specially used to render medicines more palatable and to prevent griping.

The fruit is used in Indian cookery, and its mericarps are chewed with prepared *pan* or sometimes alone to remove the after-taste of drugs.

ANET U

Dill. (Aneth.)

Syn.—Anethi Fructus Syn. I V—*Soya*, Hind.

Source.—The dried ripe fruit *Anethum graveolens*

Characters.—The fruit consists of two mericarps freed from pedicel. Each is broadly oval; 4 mm. long, 2 to 3 mm broad, compressed dorsally, brown. dorsal ridges inconspicuous, but lateral ones prolonged into *wings*. Each mericarp exhibits 6 vittæ Odour and taste, aromatic

Composition.—The *volatile oil*

OFFICIAL PREPARATION

1. Aqua Anethi Destillata—1 in 10. B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

OLEU ANETHI

Oil of Dill. (Ol. Aneth.)

Source.—Obtained by distilling Dill. Contains 43 to 63 p c. w/w of *carvone*, $C_{10}H_{14}O$

Characters.—Colour, pale yellow, odour, that of the fruit; taste, sweet, aromatic Sp gr 0.900 to 0.915 *Solubility*—In alcohol and ether.

Composition.—(1) *A Terpene (d-limonene)* *Carvone*.

B.P. Dose.—1 to 3 ms or 0.06 to 0.2 ml.

OFFICIAL PREPARATION

1. Aqua Anethi Concentrata—Oil of dill 2 p c B.P. Dose—5 to 15 ms. or 0.3 to 1 mil.

PHARMACOLOGY AND THERAPEUTICS

Dill and oil of dill are aromatics, stimulants, antiseptics, and carminatives and are used to relieve flatulence and intestinal colic. The oil corrects the griping of purgatives. Dill water is chiefly used to remove flatulence in children.

LEU ANISI

Oil of Anise. (Ol. Anis.)

Source.—Obtained by distilling dried ripe fruits of *Pimpinella Anisum*, or star-anise fruit, *Illicium verum*.

Characters.—Colourless, or pale yellow, liquid, odour, that of the fruit, taste, mildly aromatic Sp gr 0.980 to 0.994

Composition.—(1) *Anethole* 80 to 90 p c (2) *Anisic aldehyde*. (3) *Methyl chavicol*.

B.P. Dose—1 to 3 ms or 0.06 to 0.2 ml.

PHARMACOLOGY AND THERAPEUTICS

The action and uses of anise are almost identical with those of dill, except that it has a slight expectorant property and is often prescribed as a vehicle for cough mixtures.

LI NIS C TEX

Lemon Peel. (Limon. Cort.)

Source.—The fresh outer part of the pericarp of the fruit of *Citrus Lemonia*

Characters.—Outer surface, pale yellow, more or less rough, with a small amount of white spongy part of pericarp on the inner surface, numerous

large oil glands and crystals of calcium oxalate below the epidermis. Odour, characteristic, fragrant Taste, aromatic, bitter

Composition—(1) *Volatile oil* (off) (2) *Hesperidin*, a bitter principle

OFFICIAL PREPARATIONS

1 **Oleum Limonis**—Oil expressed from *Lemon Peel* A pale yellow, or greenish yellow liquid, odour that of lemons, taste, warm, slightly bitter *Sp. gr.* 0.837 to 0.861 Contains not less than 4 p c w/w of aldehydes, calculated as *citral*, $C_{10}H_{16}O$ B.P. Dose.—1 to 3 ms or 0.06 to 0.2 mil.

2 **Syrupus Limonis**—Peel 6 p c B.P. Dose—30 to 120 ms or 2 to 8 mls.

3 **Tinctura Limonis**—Peel 25 p c. B.P. Dose—30 to 60 ms. or 2 to 4 mls

PHARMACOLOGY AND THERAPEUTICS

Internally—The action of lemon peel is similar to that of orange peel. The oil is a stimulant and carminative and can be used to expel intestinal flatus. In practice both of them are used for flavouring purpose. Lemon juice is antiscorbutic and contains vitamin C

FOENICULUM

Fennel. (Fœnic.)

Syn IV—*Barī Sanf, Saurif, Hind*

Source—The dried ripe fruit of *Foeniculum vulgare*

Characters—Mericarps up to 10 mm long, 4 mm broad, small, oblong, curved, glabrous, greenish-brown or pale-yellowish brown. Odour, aromatic. Taste, aromatic, sweet. The fruit is readily separated into 2 mericarps each of which has 5 prominent primary ridges, and exhibits in transverse section 6 large vittæ.

Composition—(1) A *Volatile oil*, 3 to 4 p c which contains *anethole* and *fenchone*

Enters into—Pulv. Glycyrrhizæ Co

B.P. Dose—5 to 10 grs. or 0.3 to 0.6 grm

USES—The same as those of anise or of dill.

CINNA OMU

Cinnamon. (Cinnam.)

Syn IV—*Dalchini*, Beng and Hind *Gudatvak*, Sans. (बक और लवङ्ग)

Source—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum*.

Characters—In rolled quills, thin, brittle, splintery, light yellowish-brown; about 1 cm in diameter. Odour, fragrant Taste, warm, sweet and aromatic.

Composition—(1) *Volatile oil* (off). (2) *Tannin* (3) *Sugar*. (4) *Gum*.

B.P. Dose—5 to 20 grs. or 0.3 to 1.2 grm

Enters into—Pulv. Cretæ Arôm, Tinct. Cardam. Co

OFFICIAL PREPARATION

1 **Aqua Cinnamomi Destillata**.—1 in 10. B.P. Dose.— $\frac{1}{2}$ to 1 oz or 15 to 30 mls

OLEUM CINNA O I

Oil of Cinnamon. (Ol. Cinnam.)

Syn—Oleum Cassiæ, U.S.P

Source—The oil distilled from Cinnamon Bark

Characters—Yellowish when fresh, becoming reddish brown with age *Sp. gr.* 1.000 to 1.030 *Sinks in water*

Composition—(1) *Cinnamic aldehyde*, 50 to 65 p c (2) *Cinnamic acid* (3) *Eugenol*.
B.P. Dose—1 to 3 ms or 0.06 to 0.2 mil

OFFICIAL PREPARATION

1 **Aqua Cinnamomi Concentrata**.—Oil of cinnamon 2 p c **B.P. Dose**—5 to 15 ms or 0.2 to 1 mil.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The action and uses of cinnamon bark and its oil resemble those of cloves and the oil of cloves but the bark has besides a mild astringent property. As a flavouring and correcting agent both the bark and the oil are used. The oil is used in combination with other drugs as an intestinal antiseptic in typhoid fever. It is perhaps useful in preventing tympanitic distension.

MYRISTICA

Nutmeg. (Myrist.)

Syn. IV—*Jaiphal*, Beng., Hind

Source.—The dried kernel of the seeds of *Myristica fragrans*

Characters—Broadly oval or rounded, about 20 to 30 mm long. Externally, greyish-brown, with reticulated furrows. Internally, greyish-red marbled with brownish-red veins. Odour, strong, aromatic. Taste, aromatic, warm, bitter.

Composition—(1) A *fixed oil* consisting of glyceryl oleate, glyceryl butyrate, and glyceryl myristate, 25 to 30 p c (2) *Amylodextrin* (3) *Volatile oil*, (5 to 15 p c.).

Enters into—Pulv. Cretæ Aromat.

B.P. Dose—5 to 10 grs or 0.3 to 0.6 grm

OLEU MYRISTICÆ

Oil of Nutmeg. (Ol. Myrist.)

Source and characters—A pale yellow oil, distilled from Nutmeg, having the odour and taste of nutmeg. **Solubility**—1 in 3 of alcohol (90 p c). **Sp. gr.** 0.880 to 0.925.

Composition—(1) *Myristicin*, a terpene (3) A terpene, *α-camphene*

B.P. Dose—1 to 3 ms or 0.06 to 0.2 mil

Enters into—Sp. Ammon. Aromat., Tinct. Valerian. Ammon.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The volatile and the fixed oils are used for perfuming pomades and lotions for the hair, and diluted with olive oil or soap-liniment as an embrocation in chronic rheumatism. The expressed oil is said to possess antiseptic and antiparasitic properties. Nutmeg made into a paste is sometimes used by the people of India to remove headaches and neuralgia.

Internally.—For its agreeable aroma it is used in cooking. Both the kernel and the volatile oil are gastric stimulants, increasing the flow of gastric juice, and carminatives, expelling intestinal flatus; hence they can be used in dyspepsia, cramps and flatulence. The volatile oil relieves toothache, and the kernel is chewed to remove fœtor of breath. In large doses it acts as a powerful narcotic, causing giddiness,

vertigo and coma, symptoms resembling those that follow poisonous doses of camphor.

OLEUM LAVANDULAE

Oil of Lavender. (Ol. Lavend.)

Source—The oil distilled from the fresh flowering tops of *Lavandula officinalis*. Contains 7 to 14 p.c. w/w of linalyl acetate, $C_{11}H_{18}O_2$.

Characters—Pale yellow or yellowish-green with fragrant odour of the flowers and a pungent bitter taste. Sp. gr. 0.882 to 0.900. *Solubility*—1 in 4 alcohol (70 p.c.).

Composition—(1) *Linalol*, an alcohol, and its acetic ester, *linalyl acetate*, are the principal constituents. (2) *Pinene*, $C_{10}H_{16}$, present in some samples but is not a constant constituent. (3) *Limonene*, *geraniol* and a sesquiterpene.

B.P. Dose—1 to 3 ms. or 0.06 to 0.2 ml.

NON-OFFICIAL PREPARATION

1. *Tinctura Lavandulae Co*—Oils of lavender and rose, cinnamon bark, nutmeg, red sanders wood and alcohol (90 p.c.). *Dose*.—30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Oil of lavender is used to perfume liniments, and the tincture to colour lotions. It is an ingredient of smelling salts and lavender water.

Internally.—Like other aromatic oils, it is a stimulant, carminative and antispasmodic, and can be used in flatulence, colic, hypochondriasis, hysteria and neurasthenic affections. But the chief use of the tincture is confined to colouring and flavouring purposes.

OLEUM MENTHAE PIPERITAE

Oil of Peppermint. (Ol. Menth. Pip.)

Source—The oil distilled from fresh flowering tops, *Mentha piperita*, and rectified, if necessary. Contains 4.5 to 9 p.c. w/w *menthyl acetate*, and 46 p.c. w/w free *menthol*.

Characters—Colourless, pale-yellow or greenish-yellow when fresh, becoming darker by age. Odour of the herb. Taste, aromatic, followed by a sensation of coldness. Sp. gr. 0.902 to 0.910. *Solubility*—1 in 4 of alcohol (70 p.c.).

B.P. Dose—1 to 3 ms. or 0.06 to 0.2 ml.

Enters into—Phl. Rhei Co.

OFFICIAL PREPARATIONS

1. *Aqua Menthae Piperitae Concentrata*—1 in 50 B.P. Dose—5 to 15 ms. or 0.3 to 1 ml.

2. *Aqua Menthae Piperitae Destillata*—1 in 1000 B.P. Dose— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.

3. *Spiritus Menthae Piperitae*—1 in 10 B.P. Dose—5 to 30 ms. or 0.3 to 2 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The action of the oil of peppermint resembles that of the volatile oils generally. But owing to the presence of menthol, the sensation of coldness and numbness after a feeling of warmth is more marked. Hence, it is a local anaesthetic, and is therefore used to allay the pain of superficial neuralgias and herpes zoster. It is also a power-

ful antiseptic. It relieves toothache due to a carious tooth. The smell of the oil keeps off mosquitoes

Internally.—For its powerful antispasmodic and carminative properties, it is often used to relieve flatulent colic and spasmodic pains of the stomach. It corrects the griping effect of purgatives and covers the nauseous taste of drugs.

ZINGIBER

Ginger. (Zingib.)

Source.—The scraped and dried rhizome of *Zingiber officinale*

Characters—Flattish, irregularly branched pieces, about 7 to 15 cm long, 1.5 to 6.5 cm wide, 1 to 1.5 cm thick, each branch crowned by a depressed scar. Externally pale buff, striated, fibrous. Fracture, short, rather fibrous. Odour, well known, agreeable, and aromatic. Taste, strong, pungent.

Composition—(1) An aromatic volatile oil 1 to 3 p.c. (2) *Gingerol*, a yellowish oily body to which pungency is due. (3) Resin and starch.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Enters into—Infusum Sennæ Rec., Pulv. Jalapæ Co., Pulv. Rhei Co.

OFFICIAL PREPARATIONS

1. Tinctura Zingiberis Fortis *Syn*—Essence of Ginger. B.P. Dose—5 to 10 ms. or 0.3 to 0.6 mil.
2. Tinctura Zingiberis Mitis—1 in 5 of strong tincture. B.P. Dose—30 to 60 ms. or 2 to 4 mils.
3. Syrupus Zingiberis—B.P. Dose.—30 to 120 ms. or 2 to 3 mils.

PHARMACOLOGY AND THERAPEUTICS

Ginger is a powerful aromatic stimulant, acting like capsicum and cardamoms. Chewed, it is a valuable sialagogue; and used as snuff, it is a powerful errhine, but it is chiefly given as a stomachic, carminative and flavouring agent. Commercial gingerin, which is an oleo-resin, is a useful addition to purgative pills to prevent griping. The dose is $\frac{1}{4}$ to 3 grains.

GROUP XVIII

SOLID VOLATILE OILS (Stearoptenes)

Camphor, Menthol, Thymol

CAMP A

(Camph.)

Camphor. $C_{10}H_{16}O$

Syn. I.V.—*Karpur*, Beng. *Kapur*, *Kapur*, Hind.

Source.—Obtained from *Cinnamomum Camphora*, and purified by sublimation.

Characters.—Colourless, transparent, crystals or crystalline masses, of tough consistence; also in rectangular tablets or pulverulent masses—"Flowers of Camphor." Sp. gr. 0.995. Odour penetrating. Taste, bitter, pungent, followed by a sensation of cold. Burns and volatilises. **Solubility**.—1 in 700 of water, 1 in 1 of alcohol (90 p.c.), in 0.25 of chloroform, very soluble in ether. It forms a liquid when triturated with chloral hydrate, menthol, phenol, or thymol.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm ; 1 to 3 grs. or 0.06 to 0.2 grm. (subcutaneous)

Enters into.—Lin Terebinthinæ.

OFFICIAL PREPARATIONS

- 1 Aqua Camphoræ.—0.1 p.c. w/v. B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.
- 2 Linimentum Camphoræ. *Syn*—Camphorated Oil.—20 p.c. w/w of camphor.
- 3 Linimentum Camphoræ Ammoniatum. *Syn*.—Lin. Camphor. Co.—12.5 p.c. camphor.
- 4 Linimentum Terebinthinæ Aceticum.—Prepared with camphor liniment
- 5 Spiritus Camphoræ *Syn*.—Tinct. Camphoræ.—10 p.c. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mls.
- 6 Tinctura Opii Camphorata. *Syn*.—Tinct. Camphor Co., Paregoric.— $\frac{1}{10}$ gr. morphine in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mls.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

- 1 Linimentum Chloroformi, B.P.C.—Camphor liniment and chloroform equal quantity.
- 2 Acidum Camphoricum—A white, crystalline powder, slightly soluble in water. In *phthisical night-sweats* and *vesical catarrh*. Dose—8 to 30 grs or 0.5 to 2 grm.
- 3 Injectio Camphoræ, B.P.C.—Camphor 1, sterile olive oil to 10. Dose.—8 to 30 ms or 0.5 to 2 mls
- 4 Camphoræ Monobromata—In colourless prisms, insoluble in water. A hypnotic and nervous sedative in *hysteria*, *chorea*, *delirium tremens* and *petit mal*, also used in *spermatorrhæa*. Dose—2 to 8 grs. or 0.12 to 0.5 grm
- 5 Cardiazol.—Pentamethylenetetrazol—A water soluble complex preparation with action similar to camphor but superior in all cases of severe circulatory disturbance. May be used by mouth, subcutaneously or intravenously as an analeptic of rapid and reliable action of satisfactory duration. It stimulates the respiratory centre. Valuable in *collapse of angina*, *myocarditis* and *circulatory insufficiency*. Dose—1 c.c. subcutaneously, or 0.1 grm *per os* in tablets.
- 6 Carditone—Sodium campho-sulphonate 15 p.c. in aqueous solution. A general cardiac stimulant, also increases respiratory rate and volume. In shock, heart failure, coma, poisoning by coal gas and narcotics. Dose.—Subcutaneously, 1 to 2 c.c.; intravenously up to 2 c.c., by mouth, 25 to 100 ms (1.5 to 6 mls) per day diluted with water. This solution should not be used parenterally
7. Coramme.—Pyridine β -carboxylic acid diethylamide. A yellowish liquid, almost colourless and tasteless. Miscible with water in all proportions. Dose.—1 to 2 mls of the 25 p.c. solution, by mouth or by subcutaneous, intramuscular or intravenous injection. Valuable cardiac and respiratory stimulant, action being on the vital centres in the medulla. Specially valuable in failure of heart and respiration after excessive doses of narcotics and in bad cases of barbiturate poisoning

PHARMACOLOGY

Externally.—Camphor being a stearoptene, acts like volatile oils. It is moderately antiseptic, though weaker than many volatile oils, e.g. the coal-tar series or the phenol group of drugs. It stimulates the local vessels and causes redness and heat, thus acting as a rubefacient. It first stimulates, then depresses the local nerves producing a sensation of coolness, although the vessels are dilated.

Internally. Alimentary tract.—It has a peculiar bitter

taste and produces a sensation of coldness soon followed by that of warmth in the mouth. It stimulates the local circulation and the secretion of saliva and mucus in the mouth. In the stomach it (1) causes a sense of warmth, (2) dilates the blood-vessels, (3) increases the flow of gastric juice, and (4) stimulates the peristaltic movements and causes relaxation of the sphincters. It is therefore a gastric stimulant and carminative, but in large doses it irritates the stomach and causes nausea and vomiting. It is also an antiseptic to the intestine and relieves spasm. It is slowly absorbed and after absorption transformed into camphoglycuronic acid.

Heart and circulation—The knowledge of the action of camphor on the heart and circulation is incomplete and uncertain, although clinical experience indicates that it is a circulatory stimulant. Injected directly into the circulation it increases the arterial pressure, but this effect is not constant or persistent and often it produces no rise at all. In some experiments it has been observed to stimulate the heart, while others did not observe any change. It probably stimulates the cardiac muscle. The coronary vessels are dilated but it is not certain whether this occurs in therapeutic doses (Cushny). It has been suggested that although camphor has no action on the normal heart, it improves the heart which is depressed or irregular. It dilates the vessels of the skin and gives a sensation of warmth like alcohol. It is possible that by dilating the vessels of the skin and the coronary arteries it effects a re-distribution of the blood much in the same way as strychnine. Being an irritant when given as an injection, it provokes reflex medullary stimulation (Gunn).

Respiration.—It slightly stimulates the bronchial secretion by increasing the vascularity of the bronchial mucous membrane and acts as a feeble expectorant. The respiratory movements are hardly affected although it may be arrested during convulsion. Like other volatile oils the centre is reflexly stimulated from the stomach.

Nervous system.—It stimulates the cerebrum and in large doses produces excitement, giddiness, confusion of ideas, inco-ordination of movement and sometimes convulsion. Loss of consciousness and stupor may appear later. With some it acts as an **exhilarant**, causing agreeable hallucinations with a desire to laugh or dance, and with others no excitement is observed, the effect being one of depression with drowsiness and stupor. It first stimulates and then depresses the reflex movements and acts as an antispasmodic. The respiratory and vaso-motor centres are stimulated.

Skin.—Some dilatation of the skin vessels follows the use of camphor by the mouth, due possibly by gastric irritation. It is excreted with the sweat, which it increases.

Temperature.—It has very little effect on temperature

in health, but is a mild antipyretic in fever, due chiefly to loss of heat from dilatation of the skin vessels.

Elimination.—Camphor is partially oxidised in the tissues forming camphorol which combines with glycuronic acid and is excreted by the kidneys.

Acute toxic action.—Poisoning by camphor is rare. The writer has seen only one case of poisoning. Epigastric pain, nausea, sometimes vomiting, giddiness, dimness of sight, delirium verging on mania, epileptiform convulsions, cyanosis, paralysis, cold clammy perspiration, strangury or arrest of urinary secretion, coma and death.

Treatment—Emetics, pump, brisk saline cathartics, cold and hot douches, counter-irritation, sometimes stimulants, and strychnine hypodermically if necessary. Since alcohol and oils favour absorption, these should be avoided.

Chronic toxic action.—Young women sometimes make a habit of taking camphor regularly with a view to improve their complexion. This habit if once contracted is very difficult to shake off. Mild form of exhilaration, stupefaction, extreme weakness, and pallor are the chief symptoms.

THERAPEUTICS

Externally.—Camphor is a favourite ingredient of many liniments, for lessening the pain of fibrositis, myalgia and chronic rheumatism. The ammoniated camphor liniment and the turpentine and acetic acid liniment are effective counter-irritants in bronchitis, pleuritis and broncho-pneumonia. Camphor has been used in combination with dusting powders on eczema and intertrigo. Mixed with zinc ointment (30 grs. to 1 oz.) it allays the itching of eczema genitalis. Chloral-camphor and menthol-camphor are valuable local anodynes in superficial neuralgias

Internally. **Alimentary canal**—Mixed with chalk it is used as tooth-powder (1 in 8). Chloral-camphor relieves toothache when put into a carious tooth. Camphor water is a domestic carminative for flatulence and colic of children. Spirit of camphor may be given in flatulence and colic of adults. Very few drugs can excel camphor in summer diarrhoea and cholera. It should be given in these cases from the commencement of the illness in 5 to 6 ms. doses of the spirit every 10 or 15 minutes till the symptoms abate; and then hourly. It is useless in the later stages.

Respiratory tract.—The inhalation of camphor or its use in the form of snuff relieves coryza and that form of chronic catarrh which is characterised by paroxysmal sneezing. At the same time 5 drops of the spirit should be given by the mouth every 15 minutes. It is especially useful in chronic bronchitis if given either in the form of paregoric or in the form of a pill in combination with hyoseyamus.

Circulation.—Camphor is absorbed very slowly from the alimentary tract, it should therefore be used hypodermically as a circulatory stimulant. It is used to stimulate the heart in the later stages of infectious fevers, pneumonia, septicæ.

nia, etc. Dissolved in oil or ether (1 to 2 grs. in 1 c.c.) it is valuable in threatened failure of the heart and respiration. But many doubt its efficacy.

Nervous system.—In many spasmodic affections, such as nervous palpitation, chorea, hysteria, etc., it has been given with doubtful results.

Genital organs.—Large doses check inordinate sexual desire and chordee. Applied to the breast and given by the mouth in 3 gr. doses camphor acts as an antilactagogue.

ENT L

Menthol. $C_{10}H_{20}O$

Source.—A saturated cyclic alcohol, *p*-menthan-3-ol, obtained from the volatile oils of various species of *mentha*, or prepared synthetically.

Characters.—Colourless, acicular or prismatic crystals. Odour penetrating, resembling that of peppermint; taste, warm and aromatic, followed by a sensation of cold. **Solubility.**—Very slightly in water, readily in alcohol (90 p.c.).

B.P. Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

NON-OFFICIAL PREPARATIONS

1 **Spiritus Mentholis Compositus**, B.P.C.—Camphor, menthol, each 2 oz, terebene, eucalyptol, each 2 oz, alcohol (90 p.c.), *q s* 20 oz. **Dose**—10 drops by inhalation.

2 **Menthyl Valerianate** *Syn—Valdol*—A solution containing 30 p.c. of menthyl valerianate. A colourless liquid with an agreeable smell and no burning taste. Nervous sedative, used in *sea sickness*, *hysteria* and *neurasthenia*. **Dose.**—10 to 15 ms. either in wine or on a lump of sugar.

3 **Insufflatio Mentholis et Cocainæ**, B.P.C.—Menthol $2\frac{1}{2}$ p.c., Cocaine Hydrochloride 0.14 p.c., Ammonium Chloride, Camphor, Lycopodium. In *coryza* as a snuff.

4 **Nebula Mentholis et Thymolis Co**, B.P.C.—Menthol, camphor and phenol each 2, thymol 0.2, liquid paraffin to 100.

5 **Nebula Cocainæ Co**, B.P.C.—Cocaine 5 grm, Nebula Mentholis et Thymolis Co, to 1000. In *bronchitis*, *laryngitis* and *asthma* as a spray.

PHARMACOLOGY AND THERAPEUTICS

Locally applied menthol causes first stimulation, soon followed by a feeling of coldness, numbness and anæsthesia of the part, and thereby relieves the pain of neuralgias and other superficial pains. This is done by either drawing over the skin solid menthol, or by painting it with a liquefied preparation, such as menthol cum camphor, menthol cum chloral, or by applying a plaster. Any painting near the eyes causes a free flow of tears from the vapour. The plaster, or when used with camphor or A.B.C. liniment it is useful in rheumatic and pleurodynic pains, lumbago and sciatica. Mentholeate (menthol and oleic acid equal quantity), alcoholic solution (1 in 8), or menthol ointment (5 to 30 grs. in 1 oz. of vaseline or simple ointment) relieves pruritus. The ointment is specially useful in pruritus pudendi et ani.

Menthol, when rubbed up with either thymol, phenol, chloral hydrate, camphor or butyl chloral, forms an oily liquid, which is an excellent remedy for toothache. It should be put into the cavity of the carious tooth and covered with a pledget of absorbent cotton.

Menthol is also a powerful antiseptic and antiparasitic, and its alcoholic solution (1 in 20) is useful in ringworm of the scalp. As a snuff (menthol 5 grs. in 1 oz. of starch, talc or oxychloride of bismuth, or along with boric acid 2, and ammon. chloride 3 parts) it is efficacious in influenza, hay fever, catarrh and ozæna.

The pigment (1 to 4 of olive oil, 20 to 30 ms) has been injected into the larynx for laryngeal and tracheal tubercle and bronchiectasis with good effects; and the nebula is used as a spray in naso-pharyngeal catarrh. The anæsthetic effect lasts about 24 hours after a few injections. It is rarely used internally, except as a corrigens of griping purgative pills, and in $\frac{1}{2}$ to 1 gr. doses with extract of belladonna in flatulence and intestinal colic.

THY OL

Thymol. $C_{10}H_{14}O$

Source.—A crystalline phenol obtained from the volatile oils of *Thymus vulgaris*, of *Monarda punctata*, and of *Trachyspermum Ammi*, or prepared synthetically.

Characters.—Colourless crystals; odour, pungent, aromatic and thyme-like; taste, pungent and aromatic. Sinks in cold water. Soluble in 1000 parts of water, in 1 part of alcohol (90 p.c.).

BP Dose.— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.; 15 to 30 grs. or 1 to 2 grms. as anthelmintic

NON-OFFICIAL PREPARATIONS

1. **Volckmann's Thymol Solution**—Thymol 0.1, alcohol 2, glycerin 2, dissolve and add water to 100. As a *spray* and *antiseptic lotion*

2. **Unguentum Thymol**—In varying strengths from 5 to 30 grs. in 1 oz. of vaseline. The thymol must be dissolved in the basis by the aid of heat

3. **Liquor Thymolis Co**, B.P.C. *Syn*—*Liquor Antisepticus*.—Boric acid 29.03, benzoic acid 1.14, thymol 0.57, eucalyptol 1.25, menthol 0.38, oil of peppermint 0.31, oil of gaultheria 0.31, oil of thyme 0.31, tinct. baptisia 50, alcohol 250.0, water to 1000. Used internally as a mild antiseptic in flatulence, and diarrhoea. Diluted used as an antiseptic mouth wash. Resembles proprietary preparation *Listerine*. *Dose.*—5 to 30 ms. or 0.8 to 2 mls

PHARMACOLOGY AND THERAPEUTICS

Thymol is a very powerful antiseptic about 25 times more powerful than phenol and less toxic to the tissues, but its insolubility is its drawback. A solution of the strength of 1 in 1000 stops all putrefactive or fermentative action in any fluid to which it is added. Volckmann's solution, the gauze and the ointment are all employed in *antiseptic surgery* and the last mentioned is very useful in parasitic skin diseases, especially tinea of the scalp or beard. The pastils,

spray and inhalation are useful in laryngitis and pharyngitis.

Internally.—In large doses, thymol gives rise to very unpleasant symptoms, excitement, vertigo, etc., and the urine may become green. In still larger doses the medullary and spinal centres are paralysed, collapse sets in, and there is a marked fall of blood-pressure and temperature before death.

Its chief value, however, is as an **anthelmintic** for *ankylostomum duodenale*, for which purpose it must be given in doses of 15 to 30 grs., repeated 3 or 4 times at intervals of an hour; 60 grs. should be the maximum dose for a healthy adult, but usually 45 grs. would suffice. Such large doses however may cause abortion in women, therefore when treating pregnant women the dose should not be more than 30 grs. given in three doses of 10 grs. each. For weak, anæmic, and those with bad heart the dose should be less.

Prescribing hints.—Thymol *should not be administered in solution*, as it causes a most unpleasant burning sensation of the mouth and throat and is extremely irritating to the mucous membrane of the stomach. It should be given in pill, cachet, or emulsion. The emulsion is best made by dissolving the thymol in alcohol, and then precipitating it by pouring the alcoholic solution into cold water. A little mucilage may finally be added to keep the finely powdered thymol in suspension. The patient must keep to his bed and lie down for several hours after the last dose; he must also be warned not to partake of alcohol or any other solvent of thymol as long as the drug is in his stomach, otherwise serious consequences may ensue. It is not a suitable drug for the old or for children. It should be followed by a saline purge, and castor oil should not be used.

GROUP XIX

ANTISEPTICS, DISINFECTANTS AND PARASITICIDES

Antiseptics are substances which prevent or retard the growth of micro-organisms as long as they remain in contact with them but do not destroy them.

Disinfectants or *germicides* destroy pathogenic microbes, *i.e.* those which cause communicable diseases; *deodorants* destroy offensive or disagreeable odours.

Antiparasitics or *parasiticides* kill parasites infesting the surfaces of the body.

In dilute solutions most disinfectants act as antiseptics, yet many antiseptics while retarding the growth of micro-organisms do not act as efficient disinfectants, either because they become inert when they come in contact with organic matter, or are too poisonous to be used for a prolonged period. A large number of disinfectants, however, act upon most

forms of living matter and are *general protoplasmic poisons* and have no specific action on microbes in preference to tissues. Therefore ordinary antiseptics while destroying microbes also cause damage to the tissues in which they are lodged. Since efficient disinfection also entails destruction of the surrounding cells, it is impossible to use a drug to disinfect the tissues of the body as a whole in sufficient concentration to destroy only the microbes without injuring the tissues. Quite recently however some progress has been made in this direction. A dye compound under the name of *Prontosil* has been introduced which seems to be potent against certain bacteria and has been successfully used in the treatment of certain infection in human subjects. These compounds have unique bactericidal properties. (see Sulphanilamides, page 514).

An ideal disinfectant will exert a maximum action on the micro-organisms, *i.e. parasitotropic*, and minimum action on the body tissues, should be soluble in water or will form a uniform emulsion in all proportions, rapid in action and non-corrosive to metals. Browning and his associates have shown that certain basic substances like flavine and acriflavine act more powerfully in the presence of serum, stimulate granulating processes, are not irritating to the tissues, and do not interfere with phagocytosis. These derivatives therefore are the nearest approach to ideal antiseptics.

The exact manner in which disinfectants act is not fully understood. The degree of ionisation of a solution may have an important bearing on its disinfecting efficiency. Disinfectants act in the following ways, *viz.*—(1) by physical means, these may be of different nature, (*a*) by abstracting water, *i.e.* salt action; (*b*) heat; (*c*) sunlight and ultra-violet rays; (2) by oxidation, as potassium permanganate, hydrogen peroxide, halogen compounds; (3) by acting as general protoplasmic poisons, *e.g.* the coal-tar compounds, *etc.*; (4) by coagulating the proteins, *e.g.* the heavy metals; and (5) by acting as reducing agents, *e.g.* SO_2 . The action of mercury is due to its tendency to accumulate in the cell and on its surface by adsorption so that the microbe is surrounded by a dense layer of disinfectant (see mercury, page 465).

Antiseptics and disinfectants are classified as follows:—

Class A: General Antiseptics and Disinfectants

Class B: Intestinal Antiseptics (see page 341)

Class C: Urinary Antiseptics (see page 396)

Class D: Pulmonary Antiseptics (see page 321)

Class E: Parasitocides

General Antiseptics and Disinfectants

The drugs of this group are used for a wide variety of purposes. Apart from their use in surgical practice for

disinfecting infected wounds, the skin, or to sterilise surgeon's hands and instruments, they have a greater field of usefulness in preventive medicine. To be of value the disinfectant must be used in solution or suspension in water and the strength should be such as will not cause much irritation of the tissues or the skin. For surface disinfection the oxidising disinfectants are sufficient to destroy the microbe, but for wounds it is necessary that the drug should penetrate into the tissues to reach the organisms and this implies some destruction of the nervous structures and of the tissues in which they are imbedded causing certain amount of pain and irritation, consequently all efficient disinfectants are local irritants. Moreover some of them may be absorbed when applied to a large surface and exhibit poisonous symptoms. Owing to these effects it has been found that a wound heals less quickly when strong antiseptics are used and therefore their use is now confined only to those cases that are already infected, or there is possibility of infection, and no antiseptics are used in clean cases. In fact these heal more rapidly without the use of any antiseptics.

The general antiseptics are:—

- 1 Oxidising Agents
Hydrogen Peroxide, Potassium Permanganate
- 2 Halogens and their Compounds
Chlorinated Lime, Chloramine, Dakin's Solution, Eusol, Iodine, Iodoform
- 3 Heavy Metals
Mercury (*see* page 465), Silver Salts (*see* page 122), Copper Sulphate (*see* page 128), Ferrous Sulphate, (*see* Iron), Zinc Salts (*see* page 126)
- 4 Coal-tar Compounds
Phenol, Cresol, Resorcim, Trinitrophenol, Coal-tar, Tar, Betanaphthol, Salol, Coal-tar Dyes
- 5 Miscellaneous Compounds
Formaldehyde, Acetone, Boric Acid, Borax, Oleum Hydnocarpi, Oleum Chaulmoogræ

1. Oxidising Agents

LIQVO Y OGENII PE OXI I

(Liq. Hydrog. Perox.)

Solution of Hydrogen Peroxide. H_2O_2

Source.—Prepared by the interaction of water, barium peroxide, and dilute sulphuric acid, at a temperature below $10^\circ C$. Contains 2.5 to 3.5 p.c. w/v of H_2O_2 , corresponding to about ten times its volume of available oxygen.

Characters.—A colourless, odourless liquid with a slightly acid taste. Renders saliva frothy. Rapidly decomposes in contact with certain metals, oxidisable organic matter, also if allowed to become alkaline.

B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

NON-OFFICIAL PREPARATION

1. **Magnesii Peroxidum**—A white, tasteless powder. More stable than hydrogen peroxide. It is the chief active principle of *Magnesium Perhydrol*, which is useful in gastric and intestinal fermentation and indigestion. *Dose*—30 to 60 grs or 2 to 4 grms

PHARMACOLOGY

Hydrogen peroxide is a powerful antiseptic and disinfectant by virtue of its oxygen which it gives off when brought into contact with many substances including all forms of living matter, pus, blood, bacteria, etc. It is not an irritant and being non-poisonous is largely used. Its effects, however, last only for a short time, for as soon as the oxygen is liberated it becomes inert. When injected directly into the blood it forms gas embolism causing death of the animal.

THERAPEUTICS

Hydrogen peroxide is largely used in general and dental surgery, also many cosmetics owe their efficacy to its presence. A solution (1 in 8) may be used with benefit in sores, foul suppurating wounds, chancres and fetid discharges from the ear.

It is much employed as a gargle, or mouth wash, as in diphtheria, or pyorrhoea alveolaris, or for deeply furred tongue, and as a surgical cleanser in pus conditions. In pus cavities the oxygen is freed with great rapidity, and the pus corpuscles are said to be disintegrated.

POTASSII PER ANGANAS

(Pot Permang)

Potassium Permanganate. KMnO_4

Source.—Obtained by the action of carbon dioxide on an aqueous solution of potassium manganate. Contains not less than 99 p.c. of potassium permanganate.

Characters.—Dark purple, slender, prismatic crystals, having a metallic lustre; odourless; taste, sweet, astringent. *Solubility.*—1 in 20 of cold water.

Incompatibles.—Iodides, organic substances and any reducing agent.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 gm.

NON-OFFICIAL PREPARATIONS

1 **Liquor Potassii Permanganatis.**—1 p.c. Has a disagreeable taste. **Condy's** fluid is only of half the strength, and contains soda salt. *Dose*—120 to 240 ms. or 8 to 15 mls.

2 **Calcium Permanganate**—Gumson, deliquescent crystals, soluble in water. Useful in *enteritis* and *cholera*. *Dose*— $\frac{1}{2}$ to $1\frac{1}{2}$ grs. or 0.03 to 0.1 gm.

3 **Mangani Butyras, B.P.C.** *Syn*—*Manganese Butyrate*—1 to 15 ml of a 1 p.c. solution for injection intramuscularly at an interval of 3 to 4 days up to 3 injections. In staphylococcal, streptococcal and gonorrhoeal infections, and in acne, boils, carbuncles, etc.

PHARMACOLOGY

Externally.—Potassium permanganate in its solid form is an irritant and even caustic, and in solution a stimulant. Apart from its local action on the human body, it is a valuable oxidising agent, giving off oxygen when moist and in the presence of organic matter, thus destroying decomposing

ferments and septic germs. It is an antiseptic, deodorant and disinfectant. The only drawback is that it is expensive and yields up oxygen too quickly, rendering it inert after a short time; consequently its germicidal powers are limited.

Internally—It is an unstable compound, being decomposed into manganese dioxide in the stomach, in which form it is probably absorbed. Manganese has no direct hæmatinic property but is intimately related to iron metabolism specially in conjunction with copper, *i.e.* helps absorption of iron. When injected into the blood, or subcutaneously, it is excreted by the intestine and kidneys. Ringer considers it a useful emmenagogue.

THERAPEUTICS

Externally.—For rapidly disinfecting stools and foul discharges, washing bed-pans, articles and hands after contact with infectious diseases, for flushing water-closets and drains, potassium permanganate in solution (1 in 150) is used as an antiseptic and deodorant. Being odourless and non-irritant, it is best suited for use at the bedside. Fabrics are stained by it, but the stain is easily removed by sulphurous acid; but they must be immediately washed, otherwise they would be damaged by the sulphuric acid formed. A weaker lotion (2 grs. to 10 ozs. of distilled water) can be used as a wash for foul or suppurating ulcers, abscesses, ozæna; or as a uterine or vaginal douche after parturition or in cancer of the os. Potassium permanganate is very largely used in the local treatment of gonorrhœa. Irrigations commencing with a strength of 1 in 8000 to 1 in 6000, and subsequently rising to 1 in 4000 or even 1 in 3000 are generally used. A saturated solution (1 in 20) is an excellent application in bites by poisonous snakes and rabid dogs, if it can be immediately applied. A 5 p.c. solution can also be freely injected into the subcutaneous tissues for this purpose, but it must be noted that its contact with the virus is essential, and therefore it is useless to try it some hours after the bite has been inflicted and when the virus has entered the circulation. Its use in the bites of poisonous snakes has been strongly advocated by Lauder Brunton and Rogers.

Internally—Potassium permanganate makes a very effective gargle (2 grs. to 10 ozs. or the liquor diluted to 1 in 50) in foul and ulcerative diseases of the gums, mouth and throat. On account of its powerful oxidising property it is used to render certain poisons harmless, and therefore has been recommended in phosphorus, hydrocyanic acid, opium, morphine and other alkaloidal poisoning. As an emmenagogue it is recommended in delayed, deficient or arrested menstruation. It was claimed at one time to have a hæmatinic property, and is said to assist utilisation of iron in the formation of hæmoglobin.

Injected into the body manganese acts as a powerful stimulant to the antibody formation, and manganese butyrate is largely used in the treatment of staphylococcal infections, such as boils, furunculosis, etc. Small doses are used in conjunction with iron in the treatment of microcytic anæmia.

Rogers strongly urges the administration of a drink of calcium permanganate gr. 4 to one pint of boiled water in cholera. It may be given *ad libitum*, at the same time he administers pills of 2 grs of potassium permanganate, made up with kaolin and coated with salol, every $\frac{1}{2}$ hour until the stools become greenish in colour, and then at longer intervals. This treatment combined with injection of hypertonic saline solution has yielded brilliant results.

2. Halogens and their Compounds Chlorine, Bromine, Iodine, Iodoform

CALX CHLO INATA

Chlorinated Lime. (Calx Chlorinat)

Syn.—Bleaching Powder. Chloride of Lime.

Source.—Obtained by the action of chlorine upon slaked lime. Contains not less than 30 p.c. w/w of chlorine.

Characters.—A dull, white powder with a characteristic smell. Becomes moist and gradually decomposes on exposure to air.
Solubility.—Partly in water.

CHLORAMINA

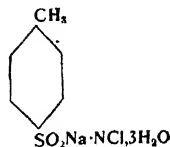
(Chloram)

Chloramine. $C_7H_7O_2NClSNa \cdot 3H_2O$

Syn.—Chloramine-T.

Source.—It is sodium *p*-toluenesulphonchloramide. Prepared by the limited action of solution of sodium hypochlorite upon *p*-toluenesulphonamide.

Characters.—White crystals, or crystalline, powder; odour, that of chlorine; taste, unpleasant, bitter. Effloresces and slowly decomposes on exposure to air, losing chlorine and assuming a yellow colour. *Soluble* in about 7 parts of water, in 2 parts of boiling water, and in 12 parts of alcohol (90 p.c.).



LIQUOR SODAE CHLORINATAE CHIRURGICALIS

(Liq. Sod. Chlorinat. Chir.)

Surgical Solution of Chlorinated Soda

Syn.—Dakin's Solution.

Source.—Prepared by combining chlorinated lime, sodium carbonate, boric acid and distilled water in proper proportions indicated in the B.P. Contains not less than 0.5 p.c. w/v and not more than 0.55 p.c. w/v of available chlorine.

NON-OFFICIAL PREPARATIONS

1. **Liquor Acidi Hypochlorosi Co** *Syn—Eusol*.—Contains approximately 0.27 p.c. hypochlorous acid with small amounts of calcium bichlorate and

calcium chloride. To 1 litre of water add 125 gms bleaching powder, shake vigorously, add 125 gms. boric acid powder and shake again, allow to stand for some hours, then filter off

Note.—Keep in stoppered bottles away from light. Deteriorates in hot weather after one week

2 *Pulvis Calcis Chlorinatæ et Acidi Borici.* *Syn* —*Eupad* — Mix intimately equal weights of finely ground bleaching powder (dry) and powdered boric acid. Contains 15 p.c available chlorine, or 11 p.c (approximately) of hypochlorous acid. Can be used as a dry dressing. The gas evolved acts more powerfully than Eusol, especially when moistened between layers of gauze or lint and covered with wool and bandaged

3 *Dichloramina, U.S.P.* *Syn* —*Dichloramine-T* — Contains 28 to 30 p.c of active chlorine. Gradually decomposes and loses chlorine on exposure to air. Pale yellow crystals or yellow crystalline powder with odour of chlorine. Almost insoluble in water

4 *Liquor Chlori (Burney Yeo)* — Put powdered potassium chlorate 30 grs. in a 12 oz bottle and pour over it strong hydrochloric acid 1 dl., cork, shake, and allow gas to generate, then add water by degrees, shaking after each addition. Into this solution dissolve 24 to 26 grs. of quinine and 1 oz of syrup of orange peel. *Dose.*—1 oz. every 3 or 4 hours in *typhoid fever*.

PHARMACOLOGY

Externally.—Chlorine has a great affinity for hydrogen, and consequently decomposes chemical and organic compounds which contain it, such as ammonia, sulphuretted hydrogen, and many organic matters. It is a powerful poison to all living matter and bacteria, but since it is a violent irritant it is not used in surgical practice except in the form of different compounds which give off chlorine more slowly. Applied to the skin for a long time as in the case of workmen in a manufactory of bleaching powder, it causes itching, redness and inflammation, leading even to vesication or sloughing. Inhaled in a concentrated form it is a powerful irritant to the respiratory passages and may cause death from spasm of the glottis or inflammation of the air-passages.

All these compounds are highly efficient disinfectants and deodorants and part with their available chlorine in a few minutes in the presence of excess of proteins, consequently their disinfectant action is very rapid. This action is a simple chemical reaction. The chlorine combines with all forms of proteins specially the amine groups forming chloramine which is a powerful antiseptic and kills any micro-organisms with which it comes into contact; but if there is an excess of protein the available chlorine is rapidly exhausted and it ceases to have any antiseptic or disinfectant property. The chloramines so formed being soluble, the hypochlorites dissolve organic matter and dead tissues. The relative action of the different preparations depends on their content of available chlorine. Chloramine solutions are more stable, neutral, less irritating and more efficacious as they do not give up the whole of the available chlorine as rapidly as the others.

Internally.—It exerts the same local influence on the

parts with which it comes in contact, until decomposed into chlorides in the stomach, when it loses its virtues as an uncombined element.

THERAPEUTICS

Externally.—As a *disinfectant* and *deodoriser*, chlorinated lime is often poured into drains, privies, urinals, bed-pans, etc. Moistened with water it may be put in saucers in different parts of a sick-room to disinfect the air. If the room requires a speedy disinfection, chlorine gas may be quickly generated by pouring sulphuric acid on salt and black oxide of manganese, the room being closed up for 24 hours. The chlorine thus liberated attacks the hydrogen of the ammonia and sulphuretted hydrogen present in the atmosphere of the room.

Chlorinated lime and liquid chlorine are largely used for sterilising drinking water and swimming baths. One drachm of bleaching powder dissolved in a pint of water and a teaspoonful of this will purify two gallons without imparting any taste to the water. For swimming baths the concentration necessary to keep the water pure is 0.2 part per million.

Eusol, Chloramine-T, and Dakin's solution are largely used as non-irritating and inexpensive antiseptics for wounds and ulcers, and for washing cavities with foul discharges, and as a nasal or vaginal injection, etc. All these compounds contain active chlorine. Since the chlorine or hypochlorite is rapidly used up by contact with the proteins of the inflamed surface, continuous saturation of wounds is necessary, and this will abolish sepsis, dissolve dead tissue and promote healing. Dakin's solution is one of the most suitable and stable forms of chlorine for this purpose.

Internally.—The different solutions are used as gargles (chloramine 0.5 p.c.) in malignant sore throat, diphtheria, mercurial salivation, and sloughing stomatitis. A solution of chlorine is recommended in septic diseases, such as typhoid fever and septicæmia, but the results are not encouraging. Burney Yeo's chlorine mixture has not proved successful in our hands, though it relieves flatulence. The great drawback to its use is its extremely nauseous taste.

IODUM

Iodine. (Iod.)

Source —Obtained from naturally occurring iodides and iodates.

Characters —Heavy, bluish-black, brittle, rhombic prisms or plates with a metallic lustre; odour, characteristic. Volatilises at ordinary temperatures. *Slightly soluble* in water, more in alcohol (90 p.c.), soluble in chloroform, ether, glycerin and carbon disulphide. Freely in solutions of iodides.

Incompatibles.—Alkalies and alkaline carbonates, oil of turpentine most volatile oils, tannin and vegetable astringents.

OFFICIAL PREPARATIONS

1. Liquor Iodi Fortis. *Syn.*—Tinct Iodi Fort., Lan Iodine.—Contains 10 p.c. w/v of iodine, and 6 p.c. w/v of potassium iodide.

2. Liquor Iodi Mitis. *Syn.*—Tinct Iodi Mitis, Tinct. Iodi.—Contains 2.5 p.c. of iodine, and 1.5 p.c. of potassium iodide, or about $\frac{1}{4}$ gr. of iodine (1 gr. total iodine) in 30 ms. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.

3. Liquor Iodi Simplex.—Contains approximately 10 p.c. w/v of total iodine, or $1\frac{1}{2}$ gr. in 15 ms. B.P. Dose.—3 to 15 ms. or 0.2 to 1 mil.

4. Liquor Iodi Aquosus. *Syn.*—Lugol's Solution, Liquor Iodi Co.—Contains 5 p.c. w/v of iodine, and 10 p.c. w/v of potassium iodide; or $\frac{1}{2}$ gr. of iodine, and about 2 gr. of total iodine in 15 ms. B.P. Dose —5 to 15 ms. or 0.3 to 1 mil.

5. Syrupus Ferri Iodidi.—Contains $7\frac{1}{2}$ grs. of ferrous iodide, equivalent to $1\frac{1}{2}$ gr. of iron in 120 ms. B.P. Dose —30 to 120 ms. or 2 to 8 mils.

NON-OFFICIAL PREPARATIONS

1. Liquor Iodi Decoloratus, B.P.C.—Iodine 28.6, Strong Solution of Ammonia 62.5, Alcohol (90 p.c.) to 1000

2. Pigmentum Iodi Co, B.P.C. *Syn.*—Mandl's Paint.—Iodine 120 gr., pot iodide 240 gr., oil of peppermint 72 ms, aqua $\frac{1}{2}$ oz, glycerin to 20 oz.

3. Entodon.—Hexamethyl-diamino-isopropional-di-iodide—A water-soluble iodine preparation. Used either *subcutaneously* or *intravenously*. Dose — $\frac{1}{2}$ to 1 ampoule or 1 to 2 c.c.

PHARMACOLOGY

Externally.—The action of iodine is identical with that of chlorine, *i.e.* it unites with amine group of proteins, with this difference that iodamines are insoluble and being less volatile, iodine is a slower bactericide than chlorine, though more lasting. Its inhalation produces irritation of the respiratory passages, cough, sneezing, frontal and thoracic pain and dyspnoea. It is a powerful antiseptic, disinfectant and antiparasitic. As an antiseptic it is superior to perchloride of mercury. It does not coagulate proteins, or form inert compound with tissues, possesses greater penetrating power, and is more stable specially when iodide is added to the solution. On the skin it is an irritant, rubefacient and vesicant, according to the strength and length of application. It stains the skin yellowish brown and deadens the cuticle which peels off. Owing to the lasting irritation of the skin there is some congestion of the subcutaneous tissues which aids absorption of exudation.

Internally.—In the stomach and intestines iodine is slowly converted into iodide and absorbed as such, but much may be left free to cause vomiting, purging and colic. It therefore produces the usual effects of iodide. It is taken up by the spleen, lymphatic glands and to a less extent by the liver. It is excreted with the urine, milk, sweat and bronchial mucus. In poisoning, gastro-enteritis may cause death from collapse and failure of heart and respiration. In minute doses it occasionally stops vomiting.

Dry thyroid contains 0.01 to 1.16 p.c. of iodine, while

other tissues contain less than 0.001 p.c. It exists in the thyroid gland as *thyroxine* and its deficiency either in the food or water produces goitre which may be improved either by the use of iodine or iodides

Toxic action.—It is generally taken in the form of tincture. Soon after swallowing there is uneasiness of the stomach with a disagreeable metallic taste followed by vomiting and severe abdominal pain. If the dose is large the pulse becomes feeble and collapse sets in. Diarrhoea follows, and the stool may contain blood. The vomit may be of iodine colour, and if the patient has taken starchy food, blue. Fatal cases are due to injection of too large quantities into serous cavities.

Treatment.—Evacuation. Demulcent drinks, chiefly starch, *e.g.* arrowroot or cooked flour. Eggs, milk and large quantities of alkalis in dilute solutions to fix the iodine. 5 p.c. solution of sodium thiosulphate may also be used. In poisoning due to injection into cysts, hydrocele, etc., very little can be done.

THERAPEUTICS

Externally.—Iodine is locally applied in subacute and chronic inflammation of joints, synovial membranes, lymphatic glands, pleura, etc. Its effects are mainly due to a mild irritant action which helps absorption of inflammation or exudation of underlying tissues or organs like other counter-irritants. Liq. iodi mitis has been successfully injected into cysts and hydroceles to induce an inflammation and adhesion of the walls and thus obliterate their cavities. Liq. iodi fortis being very strong cannot be painted more than twice or at the utmost thrice over the same spot. If the application causes much pain and irritation, the iodine can be washed off with alcohol, or with a solution of potassium iodide. It is used for the sterilisation of the skin before operations of all kinds when it penetrates readily into the pores and has a powerful germicidal action. Iodized phenol is a valuable local application in endometritis. Vapour Iodi *Ætherealis* (iodine 3 gr., ether 2 dr., phenol 2 dr., creosote 1 dr., alcohol (90 p.c.) 3 dr.) is an efficacious inhalation in chronic bronchitis and phthisis. Being antiparasitic, the mild liquor is painted over ringworm with benefit, though it causes some burning.

Internally.—The weak solution painted over the gums and teeth dissolves tartar, heals ulcers, and stimulates the growth of gums, when they have ulcerated and receded. Iodine gargle (120 to 240 ms. of the mild liquor in water 8 ozs) checks mercurial salivation, and heals syphilitic and non-syphilitic sores of the mouth and throat. Pimentum Mandl is a capital application for chronic granular pharyngitis. Liquor iodi mitis, 1 or 2 drops in 1 oz of water, at times checks vomiting when given every fifteen minutes. Iodine has been recommended in scrofula, malarial fever and gout, but without any appreciable benefit.

Iodine is used intravenously in various diseases, chiefly

plague, erysipelas, septic wounds and other streptococcal infections with much success. The usual formula is iodine gr. 24, pot iodide gr. 36, distilled water to 1 oz.; 1 c.c. being equal to 1 gr. iodine. The injections are commenced with 1 c.c. and then worked up to 5 c.c. by increasing $\frac{1}{2}$ to 1 c.c. with each injection, and are given once a week or oftener if necessary. The untoward symptoms are a rise of temperature, pain and sometimes local thrombosis.

In the form of Lugol's solution (10 ms. three times a day, in milk), it has been used in **exophthalmic goitre** apparently with some benefit. It improves nervousness, promotes sleep and appetite, slows the heart, and reduces the basal metabolism by 25 to 30 p.c. The results are not permanent for after a few weeks the symptoms return even though the treatment is continued. It is useful in that it makes the patient fit enough for surgical interference. In place of iodine, iodides may also be used. The relation of iodine in the formation of endemic goitre has led to the use of food rich in iodine, or iodised salt, as a prophylactic against the disease in endemic areas. But this treatment has been given up in favour of iodides and thyroid extract.

The use of nascent iodine has been advocated in the treatment of **pulmonary tuberculosis**.

Iodine compounds being opaque to X-rays have been used for purposes of diagnosis where bismuth or barium are inadmissible. The preparations used for the purpose are iodised oil (*see* page 323), iodophthalein (*see* page 366), and uroselectan (*see* page 403).

IO OFO MUM

(Iodof.)

Iodoform CHI_3

Source.—Prepared by the action of iodine on acetone in the presence of alkali.

Characters—Shining, lemon-yellow, small hexagonal crystals, unctuous to the touch with a characteristic, persistent and disagreeable odour and taste. Volatilises slowly. Contains not less than 99 p.c. CHI_3 . **Solubility.**—Slightly in water, in 8 parts of ether, in 10 parts of chloroform, in 100 parts of alcohol (90 p.c.), fixed and volatile oils. Soluble in 7.5 parts of benzene.

B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm.

OFFICIAL PREPARATIONS

1. **Suppositorium Iodoformi**—3 grs. or 0.2 grm. in each.
2. **Oculentum Iodoformi**—Iodoform 4 p.c.

NON-OFFICIAL PREPARATIONS

1 **Collodium c Iodoformo**—Iodoform 1, Collodion 12. As a pigment in *venereal sores and glandular swellings*.

2 **Emulsio Iodoformi**—Iodoform 10, Glycerin 70, Water 20. For injection into *sinuses and abscess cavities*.

3 **Pigmentum Iodoformi** *Syn*—*Whitehead's Varnish*—Contains Iodoform 10 p.c. in Tinct. Benzoini Co., in which ether is substituted for alcohol.

SUBSTITUTES FOR IODOFORM

1. **Thymolis Iodidum** *Syn—Aristol*—Prepared by the interaction of iodine and thymol. Contains 40 p c. of iodine. A reddish-brown powder insoluble in water and glycerin, but soluble in collodion, ether and oils. Useful in *ulcerative lupus, tinea, psoriasis*, when applied as an ointment (10 p c), or dusted, or in collodion.

2. **Iodol** *Syn—Tetra-Iodo-Pyrrol*—A brownish-white powder without disagreeable smell and toxic action, insoluble in water, but soluble 1 in 145 of glycerin, alcohol, chloroform, and ether. Externally it acts like iodoform, and internally like potassium iodide. *Dose*—1 to 4 grs or 0.06 to 0.25 gm in pill or capsule.

3. **Calcii Iodobehenas**, U.S.P. *Syn—Sajodin*.—An organic compound with calcium and iodine 23.5 p c. *Dose*, U.S.P.—8 grs or 0.5 gm.

PHARMACOLOGY

Externally—Iodoform has no special action on the skin or mucous membrane, but in susceptible persons it acts as an irritant and causes eruption to appear near the seat of the application. It is a local anæsthetic, antiseptic, disinfectant and deodorant. Pure dry iodoform is not an antiseptic and in solution it is very unstable. Since cultures of bacteria grow even in the presence of iodoform, the antiseptic action is due to the formation of iodine which is slowly evolved when it comes in contact with tissues or their extracts, particularly with diseased tissues. The iodine is liberated in an amount which does not irritate the wound, but is sufficient to prevent the growth of micro-organisms.

Internally.—The precise action of iodoform within the body is not fully understood. It is decomposed in the presence of alkaline fluids and in protein solutions, and the liberated iodine combines with the alkalies of the fluids to form iodides. After absorption iodine has been found in the saliva, sweat and bronchial secretions. But it is chiefly as iodides and partly in organic combination that iodoform is excreted in the urine. It is excreted very slowly and traces of iodides have been found for more than a month after the administration of the drug.

The symptoms of poisoning are complex and varied. A portion of iodoform circulates unchanged and gives rise to the cerebral symptoms; while other symptoms are due to the presence in the blood and tissues of iodine and iodides. The acceleration of the heart and other symptoms are due to the over-activity of the thyroid.

Toxic action.—Acute poisoning is rare now. Chronic poisoning may take place either from repeated doses, or through absorption from a raw surface. The symptoms are malaise, vertigo, dilatation of the pupil, loss of appetite, gastro-intestinal disturbance, quick, feeble pulse, fever (temperature sometimes rising to 104°F.), delirium, mania, or melancholia, erythema and perhaps eczema (iodoform dermatitis), convulsion, collapse and at times death. Fatty degeneration of the liver and muscles, hæmaturia, and albuminuria sometimes occur. These symptoms may come on suddenly, or may develop gradually, lasting for weeks. Some persons are specially susceptible to iodoform.

Treatment of iodoform poisoning.—When slight, the symptoms disappear on withdrawal of the drug. In more serious cases the symptoms appear so late that removal of the poison will not avert a fatal result. Sodium bicarbonate gr. 15 every hour prevents the formation of free iodine. Milk of magnesia 60 ms. every three hours until bowels move should be given and then once every day to keep the intestines active. Pot. brom. gr. 20 in half a tumbler of water followed by four 10 gr. doses hourly will antagonise cerebral excitement and help elimination.

THERAPEUTICS

Externally.—Iodoform is employed as a local antiseptic, but the strong characteristic smell is the chief drawback to its use. It is extensively employed in surgery in various forms such as bismuth iodoform paste (page 481), or as powder, ointment, emulsion, bougie, gauze, etc., in wounds, sloughing sores, syphilitic and scrofulous ulcers, chancres, abscess cavities, sinuses, fistulæ, etc. Collodion iodoform subdues mumps, buboes and chronic glandular enlargements. The suppository is used to relieve painful conditions of the bladder and rectum and the ointment gives great relief in *pruritus ani*. It may be insufflated for otorrhœa and frequently proves extremely beneficial.

Internally—It is rarely used internally. As a spray, pastil or insufflation, it is used in syphilitic sores of the mouth, tubercular pharyngitis, and laryngitis. It has been unsuccessfully used in gastric ulcers and phthisis; and Burney Yeo recommends $\frac{1}{2}$ gr. dissolved in cod-liver oil three times a day in tubercular peritonitis of children.

3. Coal-tar Compounds

P ENOL

Phenol. C_6H_6O

Syn.—Acidum Carbolicum; Carbohc Acid; Phenyl Alcohol.

Source.—Obtained from coal tar oil, or prepared synthetically.

Characters.—Small, colourless, needle-shaped, deliquescent crystals, becoming pinkish when exposed to moist air; odour, peculiar, but not tarry; taste, sweetish, pungent. *Solubility.*—1 in 13 of water, freely in glycerin, ether, chloroform, fixed and volatile oils, and alcohol (90 p.c.).



B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 gm.

OFFICIAL PREPARATIONS

1. **Phenol Liquefactum.** *Syn.*—*Acidum Carbolicum Liquefactum*—Contains 80 p.c. w/w of phenol. A colourless liquid, becoming pinkish on keeping. Characteristic, somewhat aromatic odour. Caustic. **B.P. Dose.**—1 to 3 ms or 0.06 to 0.2 mil.
2. **Trochiscus Phenolis.**—Each contains approximately 0.03 gm. or $\frac{1}{2}$ gr. of phenol.
3. **Glycerinum Phenolis.**—16 p.c. phenol. **B.P. Dose.**—5 to 15 ms. or 0.3 to 1 mil.
4. **Suppositorium Phenolis**—1 gr. (0.06 gm.) in each.
5. **Unguentum Phenolis.**—Phenol 3 p.c.

NON-OFFICIAL PREPARATIONS AND DERIVATIVES

1. **Sodu Phenolsulphonas, B P C** *Syn*—*Sodium Sulphocarbolate*—In colourless transparent, rhombic prisms with a saline bitter taste. Soluble in 6 parts of water. *Antiseptic* and *antipyretic*. In *diphtheria*, *cholera* and *septic fever* and in *tympanites* in preference to carbolic acid. *Dose*—5 to 15 grs. or 0.3 to 1 grm.

2. **Phenol Camphor**—Phenol 1, Camphor 3. As a local anæsthetic for toothache.

3. **Phenol Iodisatum, B P C** *Syn*—*Iodised Phenol*—Iodine 1, Liquefied Phenol 10. Caustic.

4. **Bromol** *Syn*—*Trichlorophenol*—In long silky needles, prepared by mixing a solution of phenol with bromine water. A powerful antiseptic and caustic. Internally in typhoid fever and diarrhoea. *Dose*— $\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

5. **Acidum Trichlorophenicum** *Syn*—*Trichlorophenol*—Insoluble acicular crystals, forming soluble salts with alkaline bases. Twenty-five times stronger than carbolic acid.

PHARMACOLOGY

Externally—Outside the body carbolic acid arrests the life-processes of the lower organisms, both vegetable and animal, and is a powerful parasiticide. It destroys also the properties of organised ferments, as yeast, moulds and bacteria, and prevents the zymosis of septic germs. Hence it is an antizymotic and disinfectant, though not so powerful as corrosive sublimate. As it prevents decomposition and generation of foul-smelling gases, it is an antiseptic and deodorant. Coming in contact with the serum it precipitates proteins, and being rapidly soluble in lipoids it has a greater penetrating power than many other antiseptics. It is an efficient bactericide, and in concentrations varying from 1 in 30 to 1 in 200 it kills most bacteria. Spores are more resistant to its action, so that a 5 p.c. solution takes two days to kill the spores of anthrax. Since phenol has greater affinity for oil than for water or solutions of salts in the tissues, oily solutions are less antiseptic. On the other hand its activity is increased by the addition of sodium chloride which reduces its solubility and thus helps its concentration in the micro-organisms.

Applied to the skin it is absorbed by the unbroken skin but more from a mucous surface, and causes a temporary burning and tingling followed by anæsthesia. Stronger applications act as caustic, with the formation of a white eschar without vesication. Hence, it is a local irritant, anæsthetic and escharotic.

Internally. **Gastro-intestinal canal**.—In a concentrated form carbolic acid has a similar action on the mucous membrane of the mouth, fauces, œsophagus and stomach, as on the skin. It is a powerful gastro-intestinal irritant. It is readily absorbed from the stomach and the intestine, therefore it cannot act as an intestinal antiseptic. Unorganised or chemical ferments (*enzymes*), such as pepsin, ptyalin, are not so readily affected by it except in very large doses.

Blood and circulation.—Phenol increases the rate of the heart, due probably to direct action on the cardiac muscle or on the nerves. This acceleration was formerly believed to be due to increased muscular movement and convulsions, but this view is now found to be incorrect. The heart is subsequently slowed. Injected directly into the blood it depresses the vaso-motor centre. This effect combined with the weakness and slowness of the heart causes the blood-pressure to fall. Although carbolic acid added to defibrinated blood leads to the slow formation of methæmoglobin, this change does not occur in the living animal.

Respiration.—No effect is seen in small doses, but large doses first stimulate then paralyse the respiratory centre making the respiration slow and shallow.

Temperature.—No effect is produced by medicinal doses but large ones lower it, possibly due to collapse. It is not certain whether fall of temperature is aided by some changes in the regulating mechanism.

Nervous system.—In fairly large doses it affects the medulla and cerebrum. Its influence on the respiratory, cardiac and vaso-motor centres has already been referred to. It also stimulates the salivary and sweat centres, producing salivation and perspiration. The cells of the anterior cornua are first stimulated then paralysed, the result being convulsion followed by paralysis. Poisonous doses produce headache, giddiness, contracted pupils and finally coma.

Urine.—Carbolic acid is chiefly excreted by the urine in the form of pyrocatechin and hydroquinone. Pyrocatechin being a dark-coloured body gives it a *dark or olive-green* colour but this cannot be the sole cause. The unoxidised portion combines with H_2SO_4 and is excreted as phenyl sulphuric acid which is inert. Sometimes albumin is detected. *In poisoning by phenol, the normal sulphates disappear from the urine* The glycuronates reduce Fehling's solution and the urine therefore gives rise to the suspicion of diabetes. The urine in these cases resists decomposition for a considerable time.

Elimination.—By the saliva, sweat, respiratory and gastro-intestinal secretions and urine. A portion of it is lost in the body.

Acute toxic action.—If swallowed in a concentrated form the patient feels intense burning pain in the mouth, fauces and stomach, with the formation of white eschars in the mouth, etc. He soon becomes collapsed with a cold clammy sweat, subnormal temperature, weak, feeble pulse, and shallow laboured breathing, heart and respiration stopping almost simultaneously. Reflex excitability is lost and convulsions occasionally set in. Urine becomes dark green, and finally the patient becomes insensible and comatose. Small doses cause nephritis with albumin in the urine. The *post-mortem* reveals hard, white eschars in the mouth, œsophagus and stomach with or without inflammatory redness. Blood becomes dark and its coagulability is diminished.

Treatment.—Pump, emetics. Wash out the stomach with warm water, or better first wash with 10 p.c. alcohol which dissolves the poison more readily and helps its removal. Washing must be continued till the phenol odour disappears because quite a large quantity remains in the stomach without absorption. If coma sets in, artificial respiration, caffeine and strychnine to sustain the heart. Chalk, saccharated lime, egg albumin, oils, demulcents, stimulants, hot water bottle, etc., are useful adjuvants.

Chronic toxic action.—The following symptoms have been observed by the writer in a case where a deep suppurating cavity in a scrotal elephantiasis was plugged with carbolic acid dressings, *viz.*, headache, anorexia, gastro-intestinal disturbance, insomnia, fever, dark urine.

Caution.—Green or smoky urine is often the first warning but in doubtful cases the urine should be examined to ascertain the presence or absence of ordinary sulphates. The products of carbolic acid in the urine can be detected by distilling the urine, and adding bromine water to the distillate, when white crystalline sulphocarbonate precipitates.

THERAPEUTICS

Externally.—Crude phenol is employed to disinfect and remove the foul odours of water-closets, drains, dissecting rooms, hospital-wards, bed-pans, spittoons, etc. For small operations, as for instance, puncturing the skin with a hypodermic needle, phenol may be applied to produce local anæsthesia. To stimulate indolent sores, to prevent the foul smell of gangrenous ulcers, to destroy exuberant granulations, condylomas and the poison of poisoned wounds, the application of undiluted phenol is most valuable. A 20 or 40 p.c. solution allays the itching of urticaria and eczema. To wash surgeon's hands, instruments, sponges, linen, and parts to be operated upon, carbolised lotions were extensively used in surgical practice, but its use has become very much restricted in recent years. $\frac{1}{2}$ gr. in water 5 ms. removes piles when injected. It is doubtful whether its inhalation is of any service in phthisis, gangrene of the lungs and chronic bronchitis. The application of Phenol Camphor or Iodised Phenol relieves excoriation and ulceration of the os and cervix and chronic endometritis. A vaginal douche (1 in 80 or 100) is beneficial in leucorrhœa, uterine ulcers and cancer, but it sometimes causes itching and irritation.

Internally.—For ulcerative and aphthous stomatitis, follicular tonsillitis and diphtheria the glycerin may be used as a paint, or a lotion (glycerin phenolis 15 to 20 ms. in water 1 oz.) may be used as a gargle. Subcutaneous injections of 2 to 3 p.c. aqueous solution, given every four hours, were at one time extensively used in the treatment of tetanus. As an intestinal antiseptic, phenol has been employed in enteric fever, sloughing dysentery, acute and chronic diarrhœa, but with doubtful results.

Prescribing hints.—Best given in pills. They must be

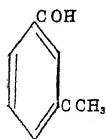
coated with keratin or varnished with salol if intended for action on the intestine. When given in a mixture it should be well diluted and combined with glycerin and peppermint water.

C ESOL

Cresol C_7H_7OH

Syn.—Acidum Cresylicum; Cresyl Hydrate.

Source.—A mixture of cresols and other phenols, obtained from coal-tar.



Characters.—An almost colourless to pale brownish-yellow liquid, becoming darker on keeping, or on exposure to light. Soluble in 50 parts of water, solution being neutral, freely soluble in alcohol (90 p.c.), in ether, chloroform, glycerin and in the fixed and volatile oils. Sp gr. 1.035 to 1.050.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 ml.

OFFICIAL PREPARATION

1. *Liquor Cresolis Saponatus*. Syn.—*Lysol*.—50 p.c.

PHARMACOLOGY AND THERAPEUTICS

Cresol is less poisonous and less toxic but more efficient germicide than carbolic acid, and may be used in the form of lotions and ointments in place of phenol. *Liquor cresolis saponatus* may be used as an antiseptic lotion for washing surgeon's hands, abscess cavities, and in obstetrical and gynaecological practice. In the form of vapour it is used in whooping cough, and other respiratory troubles, the atmosphere of the room being rendered saturated with the vapour. It is a cheap and powerful disinfectant, less poisonous than both phenol and mercurials and therefore more suitable for general use, but loses 50 to 70 p.c. of its power when it comes in contact with organic matter.

Internally it is used in keratin-coated capsules as an intestinal antiseptic but its action as such is doubtful.

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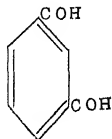
Resorcinol. (Resorcin.)

Syn.—Resorcin. Meta-dihydroxy-benzene.

Source.—Obtained by the interaction of sodium hydroxide and sodium *m*-benzene-disulphonate.

Characters.—Colourless, or nearly colourless, acicular crystals or powder. Faint odour; taste, pungent and sweetish, followed by bitterness. *Solubility*.—In less than 1 part of water, in 1 part of alcohol (90 p.c.), in ether, glycerin, and olive oil.

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 gm.



NON-OFFICIAL PREPARATIONS

1. *Spiritus Resorcinolis*, B P C Syn.—*Spiritus Capillaris*.—Resorcin 2 50, Castor Oil 2 50, Spirit of Cologne 20, Alcohol (90 p.c.) to 100 Used in dandruff and alopecia

2. *Resorcin Monacetate*. Syn.—*Euresol*.—A honey-like mass available for all

purposes for which resorcin is used, especially for application to those parts of the skin covered with hair

3. **Thio-resorcinol**—A compound of resorcin and sulphur. A yellowish powder, recommended as a *substitute for iodoform*. A 5 p.c. ointment in skin diseases.

ACTION AND USES

Resorcin is an antiseptic stronger than phenol, but less poisonous. It is used as a lotion or ointment (20 grs. in 1 oz. of zinc ointment) in psoriasis, eczema, and other irritable skin affections, as gargle in stomatitis, as spray in diphtheria and whooping cough, and as paint * in sore-throat. Andeer's lotion (resorcin 1 in water 10) is a useful application in psoriasis and chronic eczema. As a lotion it is valuable in dandruff †

Internally.—It acts as an intestinal antiseptic and is used in infantile diarrhoea, especially in combination with benzonaphthol. It is said to have a specific action comparable to quinine and has been used in hectic fevers. It should be administered well diluted with water and flavoured with syrup of orange. On account of the readiness with which it forms methæmoglobin and the danger of collapse, it should be used with caution. It is incompatible with alkalies and spirit of nitrous ether.

TRINITROPHENOL

Trinitrophenol. (Trinitrophen)

Syn—Picric Acid.

Source.—Obtained by treating phenol with sulphuric acid at a suitable temperature, and by treating the product with nitric acid. Contains not less than 99 p.c. of $C_6H_3O_7N_3$.

Characters.—Bright yellow, crystalline powder. Inodorous; taste, very bitter. Explodes when heated rapidly, or subjected to percussion. *Solubility.*—In 90 parts of water and in about 10 parts of alcohol (90 p.c.).

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

NON-OFFICIAL PREPARATIONS

1 **Ammonii Picras**—In yellow scales. Soluble in water. Useful in *ague* and *malarial fevers*. Dose $-\frac{1}{6}$ to $\frac{1}{3}$ gr. or 0.01 to 0.02 grm

2. **Unguentum Trinitrophenolis**, B.P.C.—Picric acid 2, water 2, soft paraffin 96

PHARMACOLOGY AND THERAPEUTICS

Picric acid is an irritant to the skin and mucous membranes. In large doses it causes vomiting and often anuria and strangury. After absorption it colours the skin and

*℞

Resorcin. gr. 15
Glyceri Boiacis oz. 1

†℞

Resorcin. gr. 30
Hydriac perchlor. gr. $\frac{1}{4}$
Sp ethel. ms. 30
Ol arachis ms. 30
Ol lavand. ms. 2
Aq aurant. flor ad oz. 1

mucous surfaces yellow, simulating jaundice, due to the staining of the epithelium by the acid. The saturated solution is used as a hardening agent in microscopical work. When heated with glucose it is reduced to picramic acid, and this test is utilised in the detection and estimation of glucose in urine (Johnson's test); with citric acid it forms the well known Esbach's test for albumin in urine.

It is a protoplasmic poison and precipitates proteins and acts as an antiseptic and is four times more active than phenol. Its chief therapeutic use is in cases of burns and scalds. The wounds heal under the superficial scab formed. Lint or cotton-wool soaked in 1 p.c. solution of the acid is generally used for the purpose. A 5 p.c. solution in alcohol hardens the skin and checks local sweating and is recommended for hyperidrosis of the feet. The ointment may be used in eczema, pruritus, etc.

The stains are removed by first applying powdered potassium sulphate for a minute and then washing with soap.

PIX CARBONIS PREPARATA

(Pix Carb. Præp.)

Prepared Coal Tar

Syn. I.V.—*Alkatra*, Beng.

Source.—Prepared by heating commercial coal tar in a shallow vessel and maintaining it at 50°C. for one hour, stirring constantly.

Characters.—A nearly black, viscous liquid, brown in very thin layers; heavier than water. Strongly empyreumatic odour. Almost entirely soluble in benzene and in chloroform; partially in alcohol (90 p.c.), very slightly in water.

Composition.—(1) *Benzene* and homologous hydrocarbons. (2) *Phenol*. (3) Cresols, naphthalene, anthracene, etc.

OFFICIAL PREPARATION

1. *Liquor Picis Carbonis*.—20 p.c. Is the official imitation of *Liquor Carbonis Detergens* which is an alcoholic solution of common coal tar.

PHARMACOLOGY AND THERAPEUTICS

The action and uses of prepared coal tar are identical with those of wood tar except that the former is scarcely used internally. *Liquor carbonis detergens* is the best known remedy for chronic eczema.*

PIX LIQUIDA

Tar. (Pix Liq.)

Syn.—Wood Tar; Pix Pini, U.S.P.; Pine Tar; Stockholm Tar.

Source.—A bituminous liquid, obtained from the wood of various trees of the family *Pinaceæ* by destructive distillation.

*R

Liq. carb. detergens	ms 30
Liq. plumb subacet fort	ms. 30
Hydrag. ammon.	gis 15
Paraff. moll alb	cz 1

Characters.—A dark brown or nearly black, semi-liquid substance. Odour, peculiar, aromatic. Empyreumatic taste; heavier than water.

Solubility.—In alcohol (90 p c.), in ether, and in fixed and volatile oils.

Composition.—(1) *Cresol* (2) *Phenol* (3) *Guaiacol*. (4) *Pyrocatechol*. (5) *Toluene*. (6) *Xylol*. (7) *Acetone* (8) *Resins*, etc.

B.P. Dose.—2 to 10 grs. or 0.12 to 0.6 gm.

NON-OFFICIAL PREPARATIONS

1 **Syrupus Picis Liquidæ, B.P.C.**—Tar 50 gm, sugar 850 gm, alcohol (90 p c) 525 mil, water to 1000 mls. Used in *winter cough*, *phthisis* and *chronic bronchitis*. Dose—1 to 2 dis. or 4 to 8 mls.

2 **Unguentum Picis Pini, U.S.P.**—Tar 50, yellow wax 15, petrolatum 35

3 **Potassii Hydroxyquinolini Sulphas** *Syn.*—*Chinosol*.—Yellow minute crystalline powder, readily soluble in water. Used as a surgical antiseptic, 15 gr. to the pint equals 1 in 40 of carbolic acid. Should not be used for the sterilisation of instruments, as it is apt to stain them badly.

4. **Dimol**.—A benzene derivative Dimethyl-methoxyphenol, in combination with tri- and tetra-methylphenols. A powerful bactericide, 35 p c more efficient than phenol. A valuable intestinal antiseptic. Dose—2 to 4 pulverettes after each meal.

PHARMACOLOGY

Externally.—Wood tar resembles oil of turpentine in action but is not so powerful. As it contains creosote, phenol, oil of turpentine, etc, it is an antiseptic and a vascular stimulant. When rubbed in, it sometimes causes severe inflammation or pustules, of healthy sensitive skin, specially those parts which are hairy. It is a sedative to the nerves. Tar preparations, if used for any length of time, are apt to set up a very troublesome form of acne, called by Hebra, tar acne.

Internally.—It may cause indigestion, and in large doses symptoms of carbolic acid poisoning. It is absorbed and during elimination exerts a beneficial influence on the chronically inflamed bronchial mucous membrane, disinfecting, deodorising and checking profuse secretion, and promoting free expectoration. These effects may be obtained, according to Yeo both when used as an inhalation or spray, and when taken internally.

THERAPEUTICS

Externally.—Tar water is a stimulating lotion for wounds and sluggish ulcers. The ointment is an excellent application for chronic scaly skin diseases, such as psoriasis. Chronic eczema too is benefited by it.

Internally.—As an expectorant, wood tar only is used for chronic bronchitis, bronchiectasis and winter cough. It may be given in pills, capsules, or syrup. Apomorphine combined with syrup of tar and syrup of virginian prune makes an admirable cough linctus (See page 316).

ETANAP THOL

(Betanaph.)

Betanaphthol. $C_{19}H_{17}OH$ **Syn.**— β -hydroxy-naphthalene; Naphthol.**Source.**—Prepared by the fusion of sodium naphthalene- β -sulphonate with sodium hydroxide.**Characters**—White, or nearly white, crystalline lamellæ, or powder, with odour, resembling phenol and pungent taste. *Solubility.*—1 in 1000 of cold water, 1 in 2 of alcohol (90 p.c.), in olive oil, in glycerin.**Incompatibles.**—Camphor, ferric chloride, menthol, phenazone, and phenol.**B.P. Dose.**—5 to 10 grs or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

1. **Benzonaphthol** *Syn*—*Betanaphthol Benzoate*.—A white, tasteless, insoluble powder. Intestinal antiseptic and diuretic, splitting up into β -naphthol and benzoic acid in the intestines. In *dyspepsia* and *typhoid fever*. *Dose*—5 to 15 grs. or 0.3 to 1 grm

2. **Betol**. *Syn*—*Naphthalol*, *Betanaphthol Salicylate*.—A salicylate of β -naphthol-ester. In tasteless white crystals, insoluble in water. Splits up into salicylic acid and naphthol in the system. Used in *rheumatism* and *cystitis*. *Dose.*—5 to 10 grs or 0.3 to 0.6 grm

PHARMACOLOGY AND THERAPEUTICS

Betanaphthol resembles carbolic acid in action but is not so corrosive. Naphthols irritate the mucous membrane, and when inhaled cause sneezing and coughing. They are excreted in the urine in combination with glycuronic and sulphuric acids, which give the urine a reddish-brown colour. During the course of excretion they cause pain in the bladder and urethra with strangury and swelling of the mucous membrane. It is a powerful antiseptic and disinfectant, both externally and internally. In scabies, ringworm, psoriasis and chronic eczema, the ointment (10 to 15 p.c.) having a less unpleasant odour may be used with success instead of tar, which it resembles in action. Internally it is chiefly used as a gastro-intestinal antiseptic in dyspepsia, pyloric obstruction, diarrhœa, and typhoid diarrhœa. It may be given in *cachets* or *pills*, or as an *emulsion*. The pills may be coated with keratin.

Benzonaphthol is used as an intestinal antiseptic in combination with resorcin or bismuth salicylate, in putrefactive diarrhœa, and diarrhœa of children.

In 15 gr. doses given every hour for three doses betanaphthol is an anthelmintic for *ankylostomum duodenale* and is preferable to thymol, being less irritating and cheaper. For method of treatment, *see* page 372. Both these drugs have however been replaced by oil of chenopodium (*see* page 378), and carbon tetrachloride (*see* page 376)

The use of naphthols should be avoided in irritation of the bladder, kidneys and urethra.

SALOLSalol. $C_{13}H_{19}O_3$. (Not official)**Syn**—Phenyl Salicylate**Source**—By the interaction of salicylic acid and phenol.**Characters**—Colourless crystals, with a faint aromatic odour and slight taste. **Solubility**—Almost insoluble in water, soluble in 15 parts of alcohol (90 p.c.), and in fixed and volatile oils.**Dose**—5 to 20 grs. or 0.3 to 1.2 grm.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Salol has no action on the stomach but splits up in the intestine by the fat-splitting ferment of the pancreatic juice into salicylic and carbolic acids which act as antiseptics and are then absorbed producing the usual effects. In large doses it is apt to cause *carboloria* and it should not, therefore, be given in too large doses, or for too long a period continuously, or to persons suffering from renal disease.

Its chief use is as an intestinal and urinary antiseptic and it is given with advantage both *before* and *after* all operations upon the urinary tract. As an intestinal antiseptic it is falling into disrepute.

Coal-tar Dyes

These are classified as follows:—

- 1 Acidine Dyes Acriflavine, Proflavine, Rivanol (*see* p. 513)
- 2 Azo Dyes Scarlet Red, Congo Red (*q.v.*), Pyridium (*see* p. 397)
- 3 Triphenylamine Dyes Brilliant Green, Malachite Green, Gentian Violet.
4. Fluorescein Dyes Fluoresceinum Solubile, Mercurochrome (*see* p. 468)
- 5 Phenolphthalein Dyes Iodophthaleinum (*see* p. 366)
- 6 Miscellaneous Dyes Methylene Blue, Indicarminum (*see* p. 403).

ACRIFAVINA

(Acriflavin)

Acriflavine. $C_{14}H_{14}N_3Cl \cdot HCl$

Source—It is a mixture of the hydrochlorides of 2:8-diamino-10-methylacridinium chloride and 2:8-diaminoacridine, and contains approximately one-third of its weight of diaminoacridine dihydrochloride.

Characters.—An orange-red to red, crystalline powder; odourless; taste, acid. **Soluble** in 3 parts of water, which may be precipitated by dilution or standing; in 500 parts of normal saline solution, in alcohol (90 p.c.), and in glycerin. Almost insoluble in fixed oils, volatile oils, and in liquid paraffin.

Incompatibles.—Chlorine antiseptics, phenol and corrosive sublimate solution.

B.P. Dose— $\frac{1}{2}$ to $1\frac{1}{2}$ grs. or 0.03 to 0.1 grm.

PHARMACOLOGY AND THERAPEUTICS

Acriflavine is a powerful antiseptic and has the advantage over other antiseptics in that it is not a protoplasmic poison, on the contrary it becomes more active in the presence of serum, stimulates granulating process, and does not irritate tissues, nor interfere with phagocytosis. These derivatives therefore are the nearest approach to ideal antiseptics. It is twenty times more powerful than mercuric chloride, and about eight hundred times more so than car-

bolic acid. It is extensively used in modern surgical practice as a lotion, ointment or gauze, for sores, ulcers, abscess cavities, etc. The best method is to wash out with a solution (1 in 1000 of normal saline) and then to pack with gauze steeped in the solution. In combination with tannic acid, it is used in the treatment of burns and scalds. A neutral solution, 1 in 4000 of saline, has been used as a bowel wash in ulcerative colitis, and as urethral irrigation (1 in 4000) in gonorrhœa. It is also useful in gonorrhœal infection of women. The method is to take a douche, and then lying down inject 25 c.c. of 1 in 1500 to 1 in 500 solution and retain for half an hour. This may be done twice a day.

Solution of 1 in 1000 dropped into the eye and followed by wet dressing of strong solution of magnesium sulphate and sodium chloride is valuable in gonorrhœal ophthalmia, while a solution of 1 in 4000 is useful in conjunctivitis.

It is an urinary antiseptic, and a dose of 0.2 grm. (3 grs.) administered in capsules exerts an antiseptic action on urine against both the colon bacillus and the staphylococcus, but the urine must be alkaline. It however causes unpleasant symptoms of nausea and purging in a fair proportion of cases. It is of distinct value in acute infections of the urinary tract and has been used in the treatment of gonorrhœa in doses of $1\frac{1}{2}$ grs. (0.1 grm.) given by the mouth three times a day.

It has been given intravenously in pyelitis and rheumatism (2 to 5 c.c. of 2 p.c. solution), but the results have not been very encouraging. Good results have been obtained in epidemic encephalitis when neutral acriflavine solution (10 c.c. of 0.5 p.c.) is given intravenously. To avoid unpleasant by-effects the injections should be made slowly. Improvement is noticed after three injections, and after eight injections the improvement is marked.

The stains are removed by the application of a dilute solution of sulphurous acid.

FLU ESCEINU SOLU ILE

(Fluoresc. Solub.)

Soluble Fluorescein. $C_{20}H_{10}O_5Na_2$

Source and characters.—It is the di-sodium salt of fluorescein. Prepared by the condensation of resorcinol and phthalic anhydride. An orange-red powder; odourless; almost tasteless. *Soluble* in 1 part of water, and in 5 parts of alcohol (90 p.c.).

ACTION AND USES

A 2 p.c. solution of fluorescein with 3 p.c. of bicarbonate of soda is used to diagnose corneal ulcers and abrasions. It does not stain the healthy tissue but produces a green stain when the dye penetrates any abrasion or ulcer on the eye. Similarly loss of substance in the conjunctiva produces a

yellow stain May be given by the mouth in 3 to 6 grm. doses, when it causes a yellow discoloration of the whole body which disappears in 24 hours; the normal eye is not coloured, but in intra-ocular disease, glaucoma or iritis, the aqueous humour is coloured green in about 20 minutes, while the conjunctiva remains unaffected.

Irradiated sodium fluorescein and other fluorescent salts have been used in the treatment of carcinomatous growths.* A 2 to 2.5 p c. solution of the sodium salt is painted over the affected area and part of the apparently healthy skin surrounding the growth, for two or three times, and then irradiated by X-ray or radium of moderate penetration In deep-seated growths it is given internally or intravenously before irradiation. The dose *per os* is 2 grms. in capsules or cachets of 1 grm. each.

METHYLTHIONINAE CHLORIDUM

(Methylthionin. Chlor.)

Methylene Blue $C_{16}H_{18}N_3ClS$

Source.—It is tetramethylthionine chloride Prepared by the interaction of dymethyl-*p*-phenylene-diamine with thiosulphuric acid, and subsequent oxidation. Contains not less than 80 p.c. of methylene blue.

Characters.—A dark greenish, crystalline powder with a metallic lustre, or a dull, dark-green or brown powder. Almost odourless. *Soluble* in water, in alcohol (20 p c), and in chloroform

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm

PHARMACOLOGY AND THERAPEUTICS

Externally.—Methylene blue is an antiseptic. A 3 p.c. solution is useful in tropical ulcer and as a local application for eczema in children; after application it is allowed to dry and then covered with a thin layer of collodion. A lotion (1 in 5000 to 1 in 1000) is useful as a bowel wash in dysentery and ulcerative colitis. A 5 p c. aqueous solution applied as a paint twice daily is useful in erysipelas.

Internally.—Methylene blue is an antiseptic, analgesic and antiperiodic. As an analgesic it has been used in sciatica, migraine and neuralgia with doubtful results. As an antiperiodic it has been used in malaria but is inferior to quinine and arsenic.

Since it is excreted entirely by the kidneys it is used as a disinfectant to the urinary tract before and after operation on the kidneys and prostates, in pyelitis, gonorrhœa, cystitis and other septic conditions of the urinary tract. Combined with sandal wood oil it is valuable in staphylococcal infection of the bladder, while its therapeutic activity is enhanced by combining with hexamine (hexamine 3 grs. and methylene blue $\frac{1}{4}$ gr.), when it becomes equally active in acid and alkaline urine.

*Copeman, Coke and Gouldesbrough, *B. M. J.* 1929.

It has been used in the treatment of cyanide poisoning and 50 to 100 c.c. of 1 p.c. solution has been used intravenously. The mechanism of its action is not clearly understood, although it has been suggested as being due to the formation of methæmoglobin which binds the cyanide as the stable non-toxic cyanmethæmoglobin. Others however believe that it acts by its intracellular oxidative function.

After its ingestion by the mouth it is found in large quantities in the bile, and is excreted in the urine colouring it bluish green. It has therefore been used to test the liver efficiency and the function of the kidneys. For the former 2 mg. is given before breakfast and the urine tested every 4 hours, for 12 hours. If the liver is deficient the urine will become green from 5th to 9th hour. For testing renal function, 5 ms. of a 10 p.c. solution is injected into the gluteal muscle and within 10 to 15 minutes blue jets of coloured urine should escape through the ureteral openings when observed under cystoscope. This test has been given up in favour of indigo carmine (see page 403).

As it is eliminated by the gall bladder it has been used with some success in $\frac{1}{2}$ to $\frac{3}{4}$ gr. doses in cholangitis and cholecystitis.

The usual method of administration is in cachets or capsules. To prevent gastric or vesical irritation it may be combined with nutmeg. The solution for injection should be sterilised by heating in an autoclave or by tyndallisation.

Except slight vesical or gastro-intestinal irritation no untoward effects are observed with therapeutic doses, even after prolonged use. If it is rapidly absorbed in considerable amounts, symptoms of poisoning may appear showing signs of paralysis of the heart and respiratory centres.

NON-OFFICIAL COAL-TAR DYES

1 *Proflavina*—*Diaminoacridine Sulphate*—In the form of orange-red to brownish crystalline powder. Soluble 1 in 48 of alcohol (90 p.c.), 1 in 10 or less of glycerin, insoluble in liquid paraffin. *Uses*—Similar to acriflavine but it is slightly hæmostatic.

2 *Viola Crystallina*, B.P.C. *Syn*.—*Crystal Violet*, *Gentian Violet*—It is a mixture of the hydrochlorides of penta- and hexa-methyl-paraosaniline. Introduced as an antiseptic of great value for *gram-positive organisms*. Soluble in water but solutions cannot be made with normal saline as the dye is precipitated. Used for local action in *eczematoid dermatitis*, *folliculitis*, etc. The usual formula is gentian violet grs 22, spirit rectified ms 60, aqua ad 1 oz. Used intravenously in septicæmia, endocarditis, encephalitis, etc., but the results were not striking and dangerous reaction like protein shock, may appear. *Dose*.—0.003 to 0.007 grm per kilo (\approx 3 to 7 grs for a 10-stone man) intravenously in a $\frac{1}{4}$ to 1 p.c. aqueous solution.

3 *Viride Malachitum*, B.P.C. *Syn*.—*Malachite green*, *Benzaldehyde Green*—It is oxalate of Tetra-methyl-di-para-amino-triphenyl-carbinol. A solution 1 in 2000 kills *staphylococcus aureus* in serum, and 1 in 5000 kills spores of *B subtilis*. Much used as an *antiseptic wound dressing*.

4 *Viride Nitens*, B.P.C. *Syn*.—*Brilliant green*—The sulphate of Tetra-ethyl-diamido-triphenyl-carbinol. In golden yellow crystals. Soluble in water, normal saline, and alcohol, forming a green solution. 1 in 1000 solution is much used as a *painless antiseptic dressing*. Strongly *bactericidal*.

5 **Rubrum Scarlatinum, B.P.C.** *Syn—Scarlet Red*—An azo-colouring matter of the secondary disazo group. Insoluble in water, more soluble in alcohol, and readily soluble in chloroform, oils and warm petroleum preparations. Promotes the growth of epithelium in the treatment of wounds, burns, and ulcers. Used as a dusting powder with boric acid, or as an ointment from 1 to 8 p.c.

4. Miscellaneous Compounds

LIQUOR FOR ALDEHY I

(Liq. Formaldehyd.)

Solution of Formaldehyde CH_2O

Syn.—Formalin; Formol

Source.—An aqueous solution of formaldehyde, with a variable amount of ethyl alcohol or methyl alcohol, or both. Contains 37 to 41 p.c. w/v of CH_2O .

Characters.—A colourless liquid with a characteristic pungent odour. Freely soluble in water, and in alcohol (90 p.c.)

Dispensing hints.—It should be kept in well-stoppered bottles, in a moderately warm place.

NON-OFFICIAL PREPARATIONS

1. **Amyloform**—By the action of formaldehyde on starch. An inodorous, insoluble, white powder, unaltered by heat. Used as an *antiseptic dressing for wounds*.

2. **Paraformaldehydum**—A polymer of formaldehyde, in white friable amorphous masses, slightly soluble in water, more readily soluble in hot water with formation of formaldehyde. Heated in an enclosed spirit-lamp, it sublimes, unites with the products of combustion, and is converted into formaldehyde. Has been recommended as a *disinfectant for the sick-room* after illness.

PHARMACOLOGY AND THERAPEUTICS

Formalin is a **caustic**. When diluted with ten times its bulk of water it is useful as a hardening histological agent or as a preservative for museum specimens. The solution is a powerful germicide and in dilutions of 1 in 200 kills most micro-organisms, it possibly acts by combining with some amino-group in the protein molecule. Being a powerful antiseptic, it is used for sterilising instruments, and for preservation of corpses for dissection, but on account of its necrotic action on the skin it is not suitable for treatment of wounds. It causes soft corns to shrivel up.

A solution of 1 in 500 may be used as an antiseptic gargle or mouth-wash in stomatitis, a 1 p.c. solution of the liquor is useful as a spray in diphtheria and whooping cough. A 30 p.c. solution in glycerin makes an excellent pigment in ringworm and parasitic skin diseases. Applied to sarcomata and bleeding tumours, it hardens their substances and facilitates their removal. It also lessens the fetid smell in bromidrosis of the feet.

Formaldehyde 1 part, chloroform 1 part, and alcohol 2 parts, is recommended as an antiseptic inhalation in phthisis; 5 to 10 drops being sprinkled on cotton-wool, or inhaled from the pad of an oro-nasal inhaler.

It may be used as a spray to disinfect infected rooms, or may be used as a gaseous disinfectant either by using paraform tablets or by generating the gas by adding pot. permanganas to the solution. *Paraform* requires a special apparatus, which is known as "Formogene" or "Alformant" lamp. The vapour thus produced disinfects surface only; it does not penetrate or disinfect fabrics.

Formaldehyde solution is incompatible with ammonia and all oxidising substances and renders gelatin insoluble.

ACETONUM

(Aceton.)

Acetone. Dimethyl ketone. C_3H_6O

Source and characters.—Obtained by the dry distillation of calcium acetate. A clear, colourless, transparent, mobile and volatile liquid. Odour, characteristic; taste, pungent and sweetish. Inflammable.

Dose.—60 to 90 ms. or 4 to 6 mls

ACTION AND USES

Acetone is a solvent for resin, fat, cantharidin, etc. Its action is similar to that of ethylic alcohol. A solution of iodine in acetone (1 in 50) is used to sterilise catgut. It has been used in asthma as an expectorant and antispasmodic, and as an antiseptic (with equal parts of alcohol) for sterilising the hands and site of operation.

ACIDUM BORICUM

(Acid. Boric.)

Boric Acid. H_3BO_3

Syn.—Boracic Acid.

Source.—Obtained by the interaction of sulphuric acid and native borates. Contains not less than 99.5 p.c. of orthoboric acid.

Characters.—White crystals, or powder; unctuous to touch. Odourless. Taste, slightly acid and bitter. *Solubility*.—1 in 25 of water, 1 in 4 of glycerin, 1 in 30 of alcohol (90 p.c.).

Incompatibles.—Sodium salicylate in powder forming boro-salicylate.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm

OFFICIAL PREPARATIONS

- ✓ 1. *Glycerinum Acidi Borici*. Syn.—*Glycerite of Boroglycerin*.—31 p.c. A substitute for Boro-glyceride. B.P. Dose.—10 to 30 ms. or 0.6 to 2 mls
- ✓ 2. *Unguentum Acidi Borici*.—10 p.c.

NON-OFFICIAL PREPARATION

1 *Pigmentum Acidi Borici*. Syn.—*Solutio Saturans*—Boric Acid 1, Ether 3, Alcohol (90 p.c.) 6. Used in ringworm, etc

BORAX

Borax. $Na_2B_4O_7 \cdot 10H_2O$

Syn.—Borax Purificatus; Bborate of Sodium; Sodium Borate.

Syn. I.V.—*Shohaga*. Beng, Hind

Source.—Obtained from native borax, or by boiling native calcium

borates with solution of sodium carbonate. Contains 99 to 100 p.c. of sodium borate.

Characters—Transparent, colourless, odourless, efflorescent crystals, with a weak alkaline reaction. Taste, saline, alkaline. *Solubility*.—1 in 25 of water, 1 in 1 of glycerin, insoluble in alcohol (90 p.c.). It gives a yellow colour to the flame.

Incompatibles—Mineral acids, most metallic salts, mucilage of acacia, also alkaloidal salts, *e.g.* cocaine hydrochloride.

B.P. Dose—5 to 15 grs. or 0.3 to 1 gm

OFFICIAL PREPARATIONS

1. **Glycerinum Boracis**.—12 p.c. B.P. Dose.—30 to 60 ms. or 2 to 4 mls

2. **Mel Boracis**. *Syn*—*Borax Honey*—10 p.c.

NON-OFFICIAL PREPARATIONS

1. **Nebula Alkalina Co**, B.P.C. *Syn*—*Compound Alkaline Spray*—Sod. bicarbonas 15 gms, borax 15 gms, phenol 7.5 gms, glycerin 250 mls, water to 1000 mls. As a spray or irrigation in *catarrh of the nose and throat*

2. **Pulvis Soda Chloridi Co**.—Sodium chloride 4, sodium bicarbonate 4, sucrose 4, borax 4. A saltspoonful in half a tumblerful of warm water as a gargle. Useful in *inflamed throat*

PHARMACOLOGY

Externally.—Both boric acid and borax are non-irritating and mild antiseptics. In 2½ p.c. solution almost all forms of bacilli stop growing, but they are not destroyed. They kill micro-organisms, but their action is entirely local. Some skins, however, are very sensitive to the action of boric acid, which is apt to produce a troublesome herpes in such cases.

Internally. **Gastro-intestinal tract**.—Taken by the mouth in large doses they cause gastro-intestinal irritation, evidenced by vomiting and purging. Both borax and boric acid are rapidly absorbed by the bowel, and do not affect the intestinal putrefaction.

Urinary tract.—Boric acid and borax are rapidly excreted in the urine, causing increase in the elimination of both water and urea. But the elimination becomes slow after twelve hours so that boric acid is inclined to be cumulative. Borax, like any other alkaline preparation, renders the urine alkaline. They are good genito-urinary antiseptics and differ from other more active drugs in retaining their disinfectant action when the urine is alkaline. The administration of a few doses often has a marvellous effect in rendering a foul alkaline urine perfectly clean and sweet. Repeated small doses have induced albuminuria especially in persons predisposed to it. Maximum daily dose should not exceed 60 gr.

Toxic action.—Boric acid was used as a food preservative, but owing to cases of poisoning its use has been prohibited. The symptoms are loss of appetite, mild gastro-enteritis, muscular weakness, albuminuria and prostration. The prolonged use, either internally or externally, has led to falling of the hair, eczema and psoriasis. Œdema and swelling of the skin may appear, and a gray line on the gums, similar to that seen in lead poisoning, is stated to occur along

with irritation of the mouth. Also bullous, cutaneous lesions or a dermatitis. Renal disease seems to increase the susceptibility to poisoning.

THERAPEUTICS

Externally.—Being a non-irritant, it is largely employed in surgical dressings. The ointment is applied to wounds, ulcers and burns. As its action is entirely local its use is of no value in deep suppurating cavities. It is used as an eye-wash in ophthalmia* either alone or with alum or sulphate of zinc; and as an injection in leucorrhœa, gonorrhœa, ozæna (10 grs. to 1 oz.), and otorrhœa. In cystitis, the irrigation of boric acid (1 in 100) is a capital local application. Pityriasis of the body and scalp, eczema of the ear and scalp, and cracked nipples are benefited by boric acid applications. Borax (60 gr. to water 4 ozs) removes prurigo of the labia and anus. The wearing of socks soaked in warm saturated solution of borax removes the smell of fetid perspiration of the feet.

Internally.—Borax is used as a gargle in mercurial salivation and aphthous sores of the mouth. Borax tablets slowly dissolved in the mouth reduce hoarseness. Borated tincture of myrrh is a valuable local paint for ulcerated gums, and mixed with tinct. myrrh. makes a good mouth-wash†. Mel boracis is a soothing and antiseptic application to inflamed mucous membrane and is specially useful in thrush. Borax is an excellent remedy for disinfecting foul urine. To clear putrid ammoniacal urine, boric acid is superior to borax; three or four 15 gr doses rendering it quite clear. Borax has been used to increase labour pains, and with bromides in epilepsy, but it is doubtful if it does any good.

Prescribing hints—The powder may be given in cachets or solution. Borax being alkaline should not be combined with cocaine or other alkaloids. Combined with acetate of lead or sulphate of zinc insoluble borates are precipitated. Being alkaline it liberates chloroform when prescribed with chloral hydrate.

LEU Y N CA PI

(Ol. Hydnocarp.)

Hydnocarpus Oil

Source.—A fatty oil obtained by cold expression from the fresh, ripe seeds of *Hydnocarpus Wightiana*.

Characters.—A yellowish, or brownish-yellow oil, or soft cream-coloured fat, with a characteristic odour and somewhat acrid taste. Partially *insoluble* in cold alcohol (90 p.c), freely *soluble* in hot alcohol; miscible with ether, chloroform and carbon disulphide.

*R

Acid boric.	gr	10
Alum.	gr	3
Aq dest	oz.	1

†R

Glycer borac	ms	60
Tinct. myrrh	ms.	10
Aqua	ad oz.	1

Composition.—Same as chaulmoogra oil.

B P Dose.—5 to 15 ms. increasing to 60 ms. or 0.3 to 1 ml increasing to 4 mls. For subcutaneous and intramuscular injection.—30 ms. increasing to 75 ms. or 2 mls increasing to 5 mls

OLEU HYDNOCARPI AETHYLICUM

(Ol Hydnocarp. Aeth.)

Ethyl Esters of Hydnocarpus Oil

Source.—It consists mainly of ethyl esters of chaulmoogric and hydnocarpic acids, and is produced by esterifying the fatty acids of hydnocarpus oil and ethyl alcohol, or with industrial methylated spirit

Characters.—A colourless, or faintly yellow, limpid oil, with a characteristic odour and slightly acid taste. Soluble in not less than 6 volumes of cold alcohol (90 p.c.), miscible with ether, chloroform, and carbon disulphide.

B P. Dose.—Same as hydnocarpus oil.

OLEUM CHAULMOOGRAE

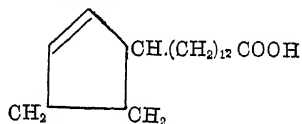
(Ol Chaulmoog.)

Chaulmoogra Oil. (Not official)

Syn—Gynocardia oil. Syn IV—*Chalmugra tel*, Beng, Hind

Source.—The fatty oil expressed from the seeds of *Hydnocarpus Kurzii*

Characters.—Brownish-yellow oil of varying consistence. Odour, characteristic. Taste, acid. Liquefies at 22° to 30° C. Solubility.—Partly in alcohol (90 p.c.), freely in ether, chloroform, carbon disulphide



Composition.—(1) Glycerides of *Chaulmoogric acid*, $C_{15}H_{31}O_2$ (2) Glycerides of *Palmitic acid* and Fatty acids. (3) *Hydnocarpic acid*

Dose—5 to 15 ms or 0.3 to 0.6 ml gradually increased to 60 ms or 4 mls. By subcutaneous or intramuscular injection—30 ms or 2 mls increased gradually to 75 ms. or 5 mls

NON-OFFICIAL PREPARATIONS

1 *Sodii Chaulmoogras*, B.P.C. Syn.—*Sodium Gynocardate*—A mixture of sodium salts of chaulmoogric acid and other fatty acids. Soluble in water. Dose.—1 to 3 gis or 0.06 to 0.2 gis

2 *Æthylis Chaulmoogras*, U.S.P. Syn.—*Ethyl Chaulmoograte*. *Moogrol*—The ethyl esters of the mixed acids of chaulmoogra oil. A clear, pale-yellow liquid, having a slight fruity odour. Insoluble in water, but miscible with alcohol, chloroform and ether. Dose, U.S.P.—By mouth or by intramuscular injection, 15 ms or 1 c.c.

3 *Sodii Hydnocarpus* Syn.—*Alepol*—Sodium salt obtained from the low melting fraction of *Hydnocarpus Wightiana* Oil. A 3 p.c. solution is given intramuscularly or subcutaneously under the skin lesions twice weekly. Dose—0.5 c.c. (of 3 p.c. solution) increased to 5 c.c. or more

PHARMACOLOGY

Externally.—Chaulmoogra oil when rubbed into the skin stimulates the local circulation and the local nerves. If rubbed too long or every day for some time, it is a rubefacient.

Internally.—Hydnocarpus or chaulmoogra oil or their ethyl esters are efficient remedies for leprosy. How they act is not clearly understood. It is believed to act by pro-

ducing a reaction with fever whereby lepra cells are ruptured and liberate the bacilli which act as antigens and increase the immunity response. The other school maintains that they increase the blood lipase which dissolves the waxy or fatty coat of the bacilli thus making them favourable for the oils to act on. It is said that in this action the large mononuclear leucocytes, which increase after an injection, assist in the transport of the oil throughout the body. While others (Walker and Sweeney) maintain that these oils, because of the presence of unsaturated fatty acids, possess a special bactericidal effect on acid fast bacilli which is the underlying cause of the specificity of these oils.

Read* found that in toxic doses the hydnocarpates produce hæmolysis of the red blood-corpuscles, renal irritation with hæmoglobinuria, anorexia, nausea and vomiting. These effects are not observed in therapeutic doses. Other effects following their use are :—

Immediate effects.—Dizziness, choking sensation and pain in the chest. Sometimes dimness or temporary loss of vision. The cause of these reactions is not known.

Local effects.—Induration, pain and abscess formation, more common after subcutaneous injections than after intramuscular injections. Regional lymph glands sometimes become enlarged or even ulcerated.

General symptoms.—Headache, malaise, fever, insomnia, anorexia, abdominal pain and a sensation of general heat. Albumin and casts, or even nephritis may appear. The so-called leprous reaction consists of fever, cutaneous eruption, neuritis, arthritis, orchitis and inflammatory reactions of the eye (iritis or iridocyclitis).

THERAPEUTICS

Formerly these oils were used by the mouth, but prolonged use in large doses upsets the stomach and therefore the ethyl esters of hydnocarpic and chaulmoogric acids are now used either intramuscularly or intravenously. The sodium salts and esters of these acids being less irritating are injected intramuscularly or intravenously. Muir recommends the following E. C. C. O. mixture as effective, convenient, and painless when given intramuscularly. It consists of ethyl esters of fatty acids of hydnocarpus oil 1 c.c., creosote (double distilled) 1 c.c., camphor 1 grm. and olive oil $2\frac{1}{2}$ c.c. Of this 0.25 c.c. is given twice a week, and gradually worked up to 2 to 5 c.c. by increases of 0.25 c.c. with each injection as long as no marked febrile or local reaction occurs. With this treatment the nodules become soft, disintegrated and eventually are absorbed, while in early cases all clinical signs disappear after treatment extending over six months.

* Journal of Pharmacology and Experimental Therapeutics, XXIV. 1924

Prescribing hints — The oral method is not so popular now. The subcutaneous injection into the diseased patches should be the method of choice. The area of the diseased skin is chosen and the needle is pushed into the subcutaneous tissue and a fraction of the mixture is injected, withdraw the needle partially and reinsert it at a different angle and inject a little more, and in this way with one insertion of the needle the drug is injected at different angles. Always inject into the loose subcutaneous tissue and not into the skin as this may cause sloughing. When large doses are required, intramuscular injections are given into the upper half of the gluteal region, care being taken to avoid the region of the sciatic nerve. Before pushing the piston home be sure that the needle has not entered a vein.

Parasiticides

Parasiticides are divided according to their action on the different varieties of parasites as follows:—

1. Tinea and its varieties: Mercury (*see* p. 465), Iodine (*see* p. 553), Phenol (*see* p. 558), Salicylic Acid (*see* p. 421), Boric Acid (*see* p. 572), Thymol (*see* p. 545), Formalin (*see* p. 571), Chrysarobin

2. Scabies or itch: Sulphur, Ichthammol, Storax (*see* p. 525), Balsam of Peru (*see* p. 525), Sandal Wood Oil (*see* p. 401)

3. Pediculi or lice: Mercury (*see* p. 465)

CHRYSA INU

Chrysarobin. (Chrysarob.)

Source.—A mixture of substances obtained from araroba, by extracting with hot benzene, evaporating to dryness and powdering.

Characters.—A light, microcrystalline, yellow, tasteless, inodorous powder. **Solubility.**—Entirely in hot chloroform and in hot benzene, slightly in alcohol (90 p.c.), almost insoluble in water.

Composition.—(1) *Chrysarobin* or *Chrysophanolanthranol*. (2) *Chrysophanic Acid*.

OFFICIAL PREPARATION

1. Unguentum Chrysarobini.—1 in 25.

NON-OFFICIAL PREPARATIONS

1. Pigmentum Chrysarobini.—Chrysarobin 1, Gutta-percha Solution 9. Dissolve. Does not stain cloth

2. Unguentum Acidi Chrysophanici (Malcolm Morris).—Acid Chrysophanic 20 gis, Paraffin Liquid 2 dis, Lanolin to 1 oz.

PHARMACOLOGY

Externally.—Chrysarobin is a powerful irritant to the skin producing a sort of erythematous inflammation. It does not irritate so much the diseased parts as the healthy skin. It destroys low vegetable growths infesting the surface of the body, and is therefore a powerful parasiticide. It is absorbed from the skin.

Internally.—Even in small doses, $\frac{1}{2}$ gr., it powerfully irritates the gastro-intestinal mucous membrane, causing ano-

rexia, vomiting and purging with gripes. It is therefore a powerful gastro-intestinal irritant.

It is eliminated chiefly by the kidneys and partly by the skin. The urine is stained purple.

THERAPEUTICS

Externally.—As a *parasiticide* it is a valuable remedy for ringworm and other forms of tinea. The B.P. ointment or the pigment are suitable preparations. It is also useful in many chronic dry skin diseases, such as psoriasis, eczema, and acne rosacea. An ointment ($\frac{1}{2}$ to 1 dr. in 1 oz. of heated soft paraffin) rubbed into the parts night and morning, acts like a charm in chronic psoriasis. Applied thus locally it also acts constitutionally, probably by absorption, since after a time patches of psoriasis to which it has never been applied also show signs of improvement and tend to disappear.

Prescribing hints.—Chrysarobin should not be applied to the face as it is apt to cause conjunctivitis, though a mild ointment (15 grs. to 1 oz.) may not produce much irritation if applied to the scalp. To prevent the irritation of the surrounding healthy skin its application should be *exclusively confined to diseased islands*. This may best be done by painting the parts with pig. chrysarobini and covering the pigment with collodion, or by applying a stiff ointment covered over with a piece of isinglass or Mead's plaster. The stains on the linen may be removed by a weak solution of potash or chlorinated lime, and partially by vegetable acids. Chrysarobin should never be applied to a large surface of the body at one time, as it may produce most unpleasant symptoms. In cases of extensive ringworm, treat the disease bit by bit, curing one patch before attacking another.

SULP U SU LI ATU

✓ (Sulphur. Sublim.)

Sublimed Sulphur.

Syn—Flowers of Sulphur.

Source.—Obtained from native sulphur, or from sulphides.

Characters.—A fine, yellow, slightly gritty powder; odourless; tasteless. Burns with a blue flame forming sulphur dioxide. *Almost insoluble* in water, in alcohol (90 p.c.), incompletely soluble in carbon disulphide

B.P. Dose.—15 to 60 grs. or 1 to 4 grm.

Enters into.—Pulv. glycyrrhizæ co.

OFFICIAL PREPARATION

✓ 1. Unguentum Sulphuris—10 p.c.

NON-OFFICIAL PREPARATIONS

1 Confectio Guaiaci Co., L.H. *Syn.*—*Chelsea Pensioner.*—Guaiacum 2, sublimed sulphur 4, mustard 4, nitrate of potash 1, rhubarb 1, honey or treacle to 64. *Dose*—60 to 120 grs. or 4 to 8 grm

2 Unguentum Sulphuris Co., B.P.C. *Syn.*—*Wilkinson's Ointment*—Soft soap 30, sublimed sulphur 15, precipitated chalk 10, tar 15, lard 30

SULPHUR PRAECIPITATUM

(Sulphur. Præcip)

Precipitated Sulphur**Syn**—Milk of Sulphur.**Source**.—Obtained by adding hydrochloric acid to a solution, prepared by boiling sulphur and lime with water.**Characters**.—A pale greyish-yellow or pale greenish-yellow, soft powder, free from grittiness, tasteless and free from odour of hydrogen sulphide. Burns with a blue flame forming sulphur dioxide. Almost insoluble in water, in alcohol (90 p.c.); almost completely soluble in carbon disulphide.**B.P. Dose**.—15 to 60 grs. or 1 to 4 grm.**OFFICIAL PREPARATION**1. **Confectio Sulphuris**—45 p.c. sulphur. **B.P. Dose**.—60 to 120 grs. or 4 to 8 grm.**NON-OFFICIAL PREPARATIONS**1. **Trochiscus Sulphuris** *Syn*—*Garrod's Lozenges*—5 grs. in each.2 **Contramine** *Syn*—*Diethyl-ammonium diethyl-dithiocarbamate*—Useful in *syphilis, arthritis, fibrositis, skin affections* and *chronic ulcers*. Prevents and ameliorates metallic poisons of various kinds. *Dose*—0.05 to 0.25 grm. ($\frac{3}{4}$ to 4 grs.) in 15 to 3 c.c. of cold sterile water or saline, intramuscularly. Must not be heated**PHARMACOLOGY**

Externally.—When applied to the whole skin pure sulphur has no effect, but if it be mixed with any greasy substance (sebaceous secretion), some of it is converted into sulphide which acts as a mild irritant, causing dilatation of vessels and in delicate skins, sometimes even severe dermatitis. Sulphide being a parasiticide, sulphur rapidly causes death of the itch insect when applied locally. When it is brought into contact with open wound, more sulphide is formed which causes more severe irritation to raw surfaces, and sometimes destruction of tissues.

Internally. **Gastro-intestinal tract**.—Being insoluble in the fluids of the mouth, sulphur has no taste, neither does it undergo any change in the stomach. When however it reaches the small intestine, it comes in contact with the alkaline bile, and a small portion being converted into an alkaline sulphide, is absorbed as such, but the greater portion passes unchanged through the bowels and is excreted with the feces. The amount absorbed depends upon the preparation used and Buchheim has shown that as much as 46 p.c. of the finely divided precipitated sulphur can be detected in the urine, but only 15 p.c. of sublimed sulphur is eliminated in this way. In the intestine sulphur acts as mild laxative, causing soft motions without any colic due to sulphides which act as mild stimulants to peristalsis. Some sulphuretted hydrogen gas is generated in the bowels which also stimulates peristalsis, but this gas forms the chief objection to its use, as the smell is very offensive.

Remote effects.—It is absorbed into the blood as sulphides and sulphuretted hydrogen which is a powerful poison, first reducing and then decomposing hæmoglobin, giving rise to marked cyanosis with coma and muscular weakness. But sulphur is never used in sufficiently large doses to produce these remote effects, but it is probable that many of the obscure nervous symptoms that accompany certain forms of dyspepsia and constipation, are due to the development of sulphuretted hydrogen gas in the bowel and its subsequent absorption into the blood.

Excretion.—Sulphur is excreted chiefly as sulphates by the urine, and as sulphuretted hydrogen by the lungs, sweat and milk. It gives an offensive smell to the breath, and blackens silver ornaments worn next the skin.

THERAPEUTICS

Externally.—Sulphur is largely used to disinfect infected rooms. For this purpose about a pound of sulphur is broken and moistened with methylated spirit and allowed to burn in a vessel. The active agent is SO_2 gas, which by acting as a reducing agent acts as a powerful disinfectant. About two pounds when burnt will give off over 2 p.c. of gas to the atmosphere of the room and will disinfect a room of 1000 cubic feet.

It is chiefly used in the treatment of scabies and itch *. If thoroughly applied it is certain in its effects and provided the strength is properly adjusted to the condition of the patient's skin no undue irritation is caused. The gritty sublimed sulphur is better as it mechanically opens up the burrows and brings the drug into closer contact with the acarus, the eggs and embryos of which lie beneath the superficial layers of the epidermis. On account of the irritation and disagreeable smell some use storax or balsam of Peru in the treatment of this disease.

If scabies be complicated by eczema and impetigo, the best preparation to use is Unguentum Sulphuris Co., B.P.C. This ointment accompanied by the use of warm bath, is applied twice daily, and cures in three days.

For the cure of acne the following lotion † is better than the ointment which is a very unsightly application to the face.

Internally.—Sulphur is largely used as a laxative, and as it causes soft motions without any pain it is specially used in hæmorrhoids and fissures of the anus, in which case it not only acts as a purgative, but it has also a direct soothing effect on the hæmorrhoidal vessels. Equal parts of the con-

*R

Acid salicylic	gr. 15
Ung sulph.	dr 4
Ung hydrarg. ammon	dr.
Ung simp	dr. 2

†R

Sulph.	gr. 60
Glycer	oz. 1
Aq. rose	oz 10

fections of senna and sulphur form a favourite prescription. Too long use of this drug leads to dyspepsia and catarrh of the bowels. It is given in plumbism to prevent reabsorption of lead from the intestines. In the form of *Chelsea Pensioner* it is a favourite remedy in chronic rheumatism and gout. It is used in many chronic skin diseases, as psoriasis, impetigo and eczema, but it is doubtful whether it does any good. Sulphur dissolved in olive oil and given intramuscularly has been recommended in arthritis deformans and chronic rheumatic polyarthritis.

POTASSA SULPHURATA

Sulphurated Potash. (Potass Sulphur.)

Syn.—Liver of Sulphur.

Source.—It is a mixture of salts of potassium, chiefly sulphides. Obtained by heating together sublimed sulphur 500 grms. and carbonate of potash 1000 grms. Contains 43.5 p.c. of total sulphur.

Characters.—Solid fragments, externally greenish-yellow, internally pale liver-brown, rapidly changing to greenish-yellow on exposure to air; odour of hydrogen sulphide. Taste, alkaline, acrid. *Soluble* in water.

NON-OFFICIAL PREPARATION

1 Calx Sulphurata.—A greyish-white powder with a smell of hydrogen sulphide. *Dose* — $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.

PHARMACOLOGY

Externally.—Both sulphurated lime and sulphurated potash are irritants and parasitocides. Sulphides, specially of calcium and barium, are valuable depilatories.

Internally.—The alkaline sulphides are easily decomposed in the stomach into sulphuretted hydrogen to which they owe their virtues. In the stomach they act as local irritants, and in the intestine stimulate peristalsis and act as purgatives. The gas however gives rise to disagreeable eructations. In small doses they merely cause a sensation of warmth in the epigastrium and determine gentle relaxation of the bowels.

The sulphides added to drawn blood reduce oxyhæmoglobin, making the blood dark venous colour, and at the same time form a combination with hæmoglobin. This compound is not formed in the blood of the living animal.

THERAPEUTICS

Externally.—Sulphurated potash in the form of an ointment* may be used in place of sulphur ointment in the treatment of scabies, but a better preparation is Lotio

(*)

Potass sulphur.	gr 60
Sod carb.	gr. 60
Ung. simp.	z 1

Calceis Sulphuratæ or Vlemineckx' solution (slaked lime 4, sublimed sulphur 4, water to 20, boil till sulphur is dissolved).

In the form of a bath (4 oz. to 30 gals. of water) sulphurated potash is used in chronic rheumatic arthritis and myalgia, chronic nervous diseases, and in chronic metallic poisoning. Sulphide baths with the internal administration of mercury constitute the celebrated Aix treatment for syphilis.

Internally.—The natural sulphurous waters are specially useful in follicular pharyngitis and are much resorted to by public singers in Europe. Sulphides are used to arrest and prevent suppuration, specially in the treatment of boils, carbuncles and scrofulous glands

IC T A M L

Ichthammol. (Ichtham)

Syn.—Ammonium Ichthosulphonate; Ichthyol.

Source.—Consists of the ammonium salts of the sulphonic acids of an oily substance, prepared from a bituminous schist, together with ammonium sulphate and water. Contains not less than 10.5 p.c. w/w of organically combined sulphur.

Characters.—An almost black, viscid liquid. *Soluble* in water, partly in alcohol (90 p.c.), miscible with glycerin and with fixed oils.

B P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

- 1 Ichthammol Collodion —1 in 8 of collodion For eczema and erysipelas.
- 2 Pasta Ichthammolis, B P C *Syn.*—*Gelatinum Ichthammol*—Ichthammol 10, gelatin 10, glycerin 60, water 25 Dries quickly and is easily washed off
3. Ichthalbin *Syn.*—*Ichthosulphol Proteinate.*—A tasteless, odourless brown powder A combination of ichthammol and albumen. In eczema and nervous intestinal affections *Dose*— $\frac{3}{4}$ to 15 grs or 0.05 to 1 gm.

PHARMACOLOGY AND THERAPEUTICS

Ichthammol contains a high percentage of sulphur, and possesses antiseptic and antiparasitic properties. As an antiseptic it is less powerful than phenol. It is a mild astringent to mucous surface and exposed tissue. An ointment (5 p.c. with lanoline), alone or combined with zinc oxide forms an excellent application in obstinate cases of ulcerative blepharitis; and a 30 p.c. ointment is used for wounds and burns of the first degree. A stronger ointment gives good results in erysipelas. It forms a valuable application in mumps and various skin diseases. To aid absorption of inflammatory products it is used in gynaecological practice as tampons with glycerin (5, 10 or 20 p.c.).

In conjunction with conium (page 250) it forms a valuable application in hæmorrhoids, either in the form of a suppository (3 grs. in each) or as an ointment.

It has been used internally as an intestinal antiseptic, and in rheumatism and other skin affections

NUTRIENTS

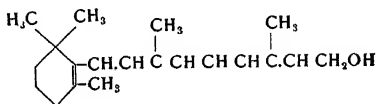
VITA INS

These accessory substances are of diverse nature although they are grouped together under the name of *vitamins*. They are essential to the normal growth and health. The part they play in the metabolism is not clearly understood and since very minute quantities are required for the maintenance of health, it has been suggested that they stimulate the production of hormones and are not directly concerned in the nutrition of body cells or the general growth of the organism.

Vitamins exist in the foods in very minute quantities, and a vitamin free diet gives rise to certain diseases, generally known as deficiency diseases, and may even cause death. Rickets, pellagra, scurvy, beri-beri, xerophthalmia or keratomalacia, osteomalacia are some of the diseases caused by the lack of vitamins in the food. Green vegetables and fruits are rich in vitamins, and both man and animals obtain their vitamins from these sources. Vitamins are produced only in plants, from which they pass directly with vegetable foods, and indirectly with animal foods, into the system.

Syn.—Growth promoting factor; Anti-infective factor; Fat-soluble A.

Source and characters.—It is present in the yellow pigment of plant and occurs in the form of pale yellow needles, and it is known to be formed in the animal body from the carotenoid pigment β -carotene. Carotene is a hydrocarbon and occurs in three forms, viz *alpha*, *beta* and *gamma* carotene, and cryptoxanthine, a closely related pigment found in yellow maize. Its main sources are (a) certain fats of animal and vegetable origin; (b) chlorophyll in green vegetables. It is also found in milk, cream, butter, beef-fat, cod-liver



oil, halibut-liver oil, and other fish oils, mammalian liver, and yolk of eggs. Carotene is thermostable but is destroyed by acids, oxidising agents and ultra-violet light.

The international unit of vitamin A is the specific activity contained in 0.6 microgram (0.6 γ) of the standard preparation of β -carotene. Pure vitamin A has an activity of 3,000,000 units per gram.

Vitamin A is essential for maintaining the integrity of the epithelial linings throughout the body and the proper structure and function of the nervous system. Its deficiency (a) retards growth and lowers resistance, either local or general, to bacterial infections; (b) causes xerophthalmia or inflammation of the eye; (c) retards regeneration of the visual purple and helps development of night blindness; (d) decreases the number of blood platelets; (e) produces atrophy of the cells of the salivary glands, mucous membrane of the intestine and of the intestinal villi; (f) causes dryness of the skin due to keratinisation of epithelial tissues, and a tendency to papular eruption; (g) causes paralysis of various types from demyelination of the spinal cord; (h) helps development of pyorrhœa alveolaris in dogs; and (i) helps formation of phosphatic calculi.

Vitamin A has been synthesised but is not yet available for therapeutic use.

Mellanby has suggested that the paralysis associated with famine, *e.g.* convulsive ergotism, may be the result of the absence of this vitamin.

Human requirement of vitamin A daily is 2,000-4,000 units for adults; 6,000-8,000 units for children; and 5,000 for pregnant women.

VITA IN C PL X

Vitamin B is water soluble and is supposed to contain six separate entities, the important ones are vitamin B₁ and vitamin B₂.

Vitamin B factors are found to some extent in all natural food-stuffs, specially in the germ and outer layers of cereals and legumes, in yeast and nuts, tomatoes, green leaves, fish, meat, eggs and milk. It is found in abundance in rice polishings, branny coat of wheat and oatmeal.

PULVIS VITA INI

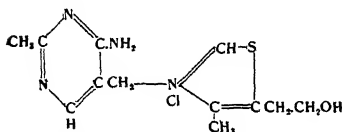
Adsorbate of Vitamin B₁. (Pulv. Vitamin. B₁)

Syn.—Aneurin.

Adsorbate of vitamin B₁ is an adsorbate of the antineuritic vitamin (vitamin B₁) upon fuller's earth. It contains in 1 gram. 100 Units of antineuritic activity (vitamin B₁).

May be prepared from rice polishings, yeast, wheat embryo, or other suitable materials.

Characters—A cream-coloured powder; almost odourless; tasteless. Insoluble in water, and in mineral acids.



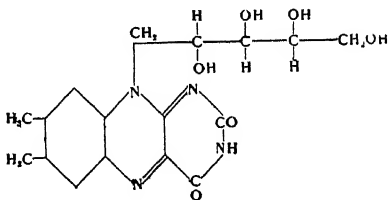
B.P. Dose.—*Prophylactic (daily)* :—15 to 30 grs. or 1 to 2 grm. (100 to 200 Units) *Therapeutic (daily)* :—30 to 90 grs. or 2 to 6 grms. (200 to 600 Units).

Vitamin B₁ has been isolated and synthesised as a white crystalline powder. It is amino-peptide hydrochloride containing Cl, N and S. Its physiological activity is identical with the natural product. It is less stable than vitamin A, not oxidised in air, and is destroyed by alkalis.

Deficiency of this vitamin causes beriberi in man and analogous disease in animals. This is characterised by anorexia, loss of flesh and strength, polyneuritis, oedema, and bradycardia. Its absence prevents the oxidation of pyruvic acid so that there is an accumulation of lactic and pyruvic acids (intermediate products of carbohydrate metabolism) with the result that the nerve cells fail to function normally. It further causes malnutrition and production of intestinal stasis with retention in the bowels of the putrid food residue and absorption of the products of putrefaction. Minor degree of deficiency in children causes retarded growth, poor appetite, constipation, neuritic pains and tenderness. It follows therefore that any of these conditions will be benefited by the administration of the official preparation or by giving foods rich in this vitamin. It has also been found valuable in various types of neuritis, specially toxic neuritis, *e.g.* alcoholic, lead or arsenic; vomiting of pregnancy; atonic constipation, etc. In urgent and bad cases intramuscular or intravenous administration of some pure synthetic preparation, *e.g.* *Betaxan* may be given. Each ampoule of 1 c.c. contains 2 or 10 mg (1 mg. is equal to 500 units)

The international unit is defined as the antineuritic potency of 10 mg. of the adsorbate. Pure crystalline vitamin B₁ has an activity of 500 international units per mg. The pure crystalline substance has not been adopted as a standard.

Vitamin B₂ is composed of two factors: riboflavine, which is responsible for the growth promoting properties, and another which is pellagra preventive, p-p factor (part of original vitamin B₂). Riboflavine is a water soluble pigment first isolated from milk (lactoflavine) but also found in yeast and liver extract.



Vitamin B₂ is essential for normal growth of the cutaneous or epithelial tissues of all kinds, and its deficiency shows retardation of growth, loss of weight and appetite, dermatitis, scaliness and baldness, neuritis and anæmia, glossitis and symptoms resembling pellagra. The antipellagra factor was formerly thought to be vitamin G. But the

p-p factor of Goldberger is closely related to *Nicotinic Acid*. The amide of nicotinic acid is part of the molecule of co-enzyme co-*zymase*, which plays an important part in the carbohydrate breakdown. Vitamin B₆ is the rat antidermatitis factor.

Vitamin B₂ complex also contains an anti-anæmic factor which cures pernicious anæmia. This is possibly the "extrinsic factor" or a substance related to it which combines with the "intrinsic factor" of the gastric mucous membrane and forms the anti-anæmic factor. For the supply of this factor yeast extract or marmite is used.

Nicotinic Acid.—Supplied in the form of tablets for oral use or in the form of ampoules for hypodermic administration. Each tablet contains 50 mg. *Dose*.—10 tablets daily (curative); 1 tablet once or twice daily after food (prophylactic). Each 1 c.c. ampoule contains 50 mg.

CE EVISIAE FER ENTU

Yeast. (*Not official*)

Syn—Faex Medicinalis Beer Yeast. *Saccharomyces Cerevisiæ*.

Characters.—A viscid, frothy liquid, having a peculiar odour and bitter taste.

Composition—Several enzymes, (1) *Zymase*, which decomposes monosaccharides into alcohol and CO₂, (2) *Invertase*, which inverts sugar, (3) *Maltase*, converts maltose into dextrose, and (4) *Endotryptase*, a proteolytic enzyme. Fats, *ergosterol*, various carbohydrates, and various proportions of proteins combined with nucleic acid forming nucleins and nucleo-proteins, (5) *Water-soluble vitamin B complex*

Dose—Of compressed yeast, ¼ to ½ oz. or 8 to 16 grm., of dried yeast, ½ to 1 dr. or 2 to 4 grm.

NON-OFFICIAL PREPARATION

1 **Nuclein** *Syn.*—*Nucleol.*—Obtained from yeast. A combination of nucleic acid with albuminates and carbohydrates. *Dose*—15 grs. several times daily. Recommended in *tuberculosis*, *cancer* and various *septicæmic conditions*. Its value is doubtful. Tablets—1 gr.

PHARMACOLOGY AND THERAPEUTICS

Yeast soap or yeast combined with ichthammol and salicylic acid is useful in acne and dermatitis.

The action of yeast is that of nuclein and it is both a leucocyte-stimulant and bactericide. It is credited with some power to neutralise toxins present in the blood. Both brewer's and compressed yeast are gastro-intestinal antiseptics, increase intestinal peristalsis, clear the tongue and aid in combating streptococcic and staphylococcic infections. In addition to *nuclein*, yeast contains many *enzymes*, and it gives rise to many other products, partly as a result of fermentation and partly by its action upon the metabolism of liver cells, and is supposed to diminish sugar in diabetes. It has been recommended in the treatment of furunculosis (both by mouth and locally), gastro-enteritis, and constipation. Being rich in *vitamin B complex* it is used in *beri-beri*. Yeast may be used either with meals or on an empty stomach, suspended in water or orange juice. The yeast cake may be used in solution in water; the dose being half to one-third of a cake. It may also be administered either in the crude form as obtained from the brewers, or as Marmite. Because of the presence of *ergosterol*, yeast when irradiated with ultra-violet light, acquires anti-rachitic properties owing to the conversion of *ergosterol* into vitamin D. The use of marmite has been extolled in the treatment of *macrocytic hyperchromic anæmia*, specially the anæmia of pregnancy. Since dried yeast, or watery extract of yeast, is therapeutically inactive as a source of Castle's extrinsic factor, but autolysed yeast

ASCORBIC ACID

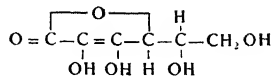
products are active, it has been suggested that the principle in yeast active in the treatment of tropical macrocytic anæmia is identical with the extrinsic factor.

ACIDU ASCO BICUM

Ascorbic Acid. (Acid. Ascorb.)

Syn.—Vitamin C; The Antiscorbutic Factor; Cevitamic acid.

Source—It is the enolic form of 3-keto-*l*-gulofurano-lactone. Obtained from the ripe fruit of *Capsicum annuum*, and other vegetable sources, or by synthesis. Contains not less than 98 p.c of $C_6H_8O_6$.



Characters.—Minute colourless crystals; odourless; taste, acid, resembling that of lemon juice. Readily soluble in water; less soluble in alcohol (95 p.c), in methyl alcohol, and in acetone.

Storage.—It is stable when kept in a glass bottle. Solution of ascorbic acid, specially if alkaline, deteriorates rapidly in contact with air.

B.P. Dose.—*Prophylactic (daily)*:— $\frac{1}{2}$ to $\frac{1}{4}$ gr. or 0.025 to 0.05 gm. (500 to 1000 Units). *Therapeutic (daily)*:— $1\frac{1}{2}$ to 4 grs. or 0.1 to 0.25 gm. (2000 to 5000 Units).

Ascorbic acid possesses antiscorbutic properties and, if tested by the *biological assay of antiscorbutic vitamin (vitamin C)*, contains in 1 gm. 20,000 Units of antiscorbutic activity (vitamin C).

This vitamin is water-soluble and its richest sources are cabbages, turnips, lemons, oranges and tomatoes. It is less widespread than vitamin B but is more sensitive to heat and drying. It has been isolated in the pure form from fruit juice, and has also been synthetically prepared.

It regulates the intracellular cement substance of capillaries; promotes the growth and ripening of the red and white blood cells and increases the blood platelets; and with vitamin D regulates the calcium metabolism. Its deficiency leads to malnutrition, loss of weight, degeneration of capillary walls and symptoms of scurvy with decalcification and loosening of the teeth, pyorrhœa, and bleeding from the gums. It also produces anæmia, anorexia, subcutaneous hæmorrhage, degeneration of skeletal muscle and necrotic foci in the liver.

Administration of ascorbic acid not only prevents but also helps to cure infantile and adult scurvy. In mild cases administration of foods rich in this vitamin, e.g. lemon juice, oranges, etc. will cause improvement. But in severe cases ascorbic acid should be given, and if necessary hypodermically or intravenously. As the solution is acid with a pH of about 2.5 it will cause local necrosis with sterile abscess when given hypodermically, and hæmolysis when given intravenously. It should be given dissolved in normal saline solution (50 to 100 mg in 5 c.c) and neutralised immediately before use with half its weight of bicarbonate of soda.

Recently it has been asserted that deficiency of this

vitamin is a potent factor in delaying healing of wounds, and McConkey and Smith have shown that peptic ulcer is very apt to occur in animals when in a state of vitamin C deficiency. Its use has therefore been advocated in the treatment of peptic ulcer and ulcerative colitis.

To prevent symptoms of pre-scorbutic condition, children should get about 50 mg. or 1,000 international units daily.

It has been used in capillary bleeding, allergic conditions, psoriasis, microcytic hypochromic anæmia, rheumatoid arthritis, arsenical dermatitis, and whooping cough.

VITA IN

It is a fat-soluble vitamin with antirachitic properties and splits up into D₁, D₂, and D₃, all of which have been shown to possess antirachitic properties. Of these vitamin D₂ has been recognised under the name "Calciferol". They are all sterol compounds and are therefore related to the male and female sex hormones (*see* page 422) and to many of the cardiac glycosides.

It occurs mostly with vitamin A and at one time it was considered to be the same. It is found in abundance in cod-liver oil, halibut-liver oil and other fish oils. It is also present in milk, cheese, meat, butter, yolk of eggs. In the body it is formed by the action of ultra-violet rays or direct sunlight on the skin. Similarly it is prepared by the action of ultra-violet rays on ergosterol, milk, yeast and other foods.

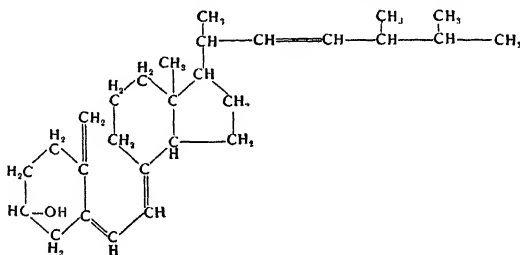
Deficiency of this vitamin causes rickets and defective calcification of teeth from lack of absorption of calcium or phosphorus. It increases the power of the blood to carry more calcium and phosphorus in balanced proportions to be deposited on the bones. It is possible that it helps absorption of calcium by reducing the alkalinity of the intestinal contents by forming soluble calcium soap or acid calcium phosphate. It was once thought that the action of this vitamin depended upon the integrity of the parathyroid glands. It is however now believed that it increases the serum calcium by promoting absorption from the intestine, whereas parathyroid extract raises blood calcium by mobilising calcium and phosphate from the soft tissues and bones.

CALCIFEROL

Calciferol. C₂₈H₄₃OH

Source—It is prepared by the ultra-violet radiation of ergosterol in a suitable solvent. The product of the irradiation, after removal of the solvent, is dissolved in alcohol (95 p.c.) or other suitable organic solvent, and strongly cooled. The unchanged ergosterol is then subjected to a complicated process of filtration, crystallisation and recrystallisation when pure crystals of calciferol are formed. 1 milligram contains 40,000 Units of antirachitic activity (vitamin D).

Characters.—Colourless, acicular crystals; odourless Insoluble in water, readily soluble in alcohol (95 p.c.), in ether, in chloroform, and in acetone; soluble in 50 to 100 parts of vegetable oils.



Storage.—It should be stored in hermetically sealed glass containers, from which air has been evacuated or replaced by an inert gas, protected from light, and stored in a cool place

B.P. Dose.—*Prophylactic (daily) for an infant*:— $\frac{1}{2500}$ to $\frac{1}{1000}$ gr. 0.025 to 0.05 mg. (1000 to 2000 Units). *Therapeutic (daily) for an infant*:— $\frac{1}{1250}$ to $\frac{1}{500}$ gr. or 0.05 to 0.075 mg. (2000 to 3000 Units).

OFFICIAL PREPARATION

1. **Liquor Calciferolis.**—It is a solution of calciferol in oil. Contains in 1 grm. 3000 Units of antirachitic activity (vitamin D).

B.P. Dose.—*Prophylactic (daily) for an infant*:—5 to 10 ms. or 0.3 to 0.6 mil (1000 to 2000 Units). *Therapeutic (daily) for an infant*:—10 to 15 ms. or 0.6 to 1 mil (2000 to 3000 Units). Contains 3000 units in 15 ms. or 1 mil.

USES

The utility of vitamin D has been fully discussed. Calciferol possesses antirachitic property of great power. It favours the absorption of calcium and the retention of bone forming salts in the body. In rickets the calcium and phosphorus are absorbed but the body is not able to deposit them on the bones, but these are re-excreted so that a negative balance results. Administration of calciferol or some form of vitamin D prevents this loss, and it is possible that it helps not only the absorption but retention of the bone forming salts by altering the reaction of the gut to acid. Calciferol is therefore used not only for the treatment of rickets but also as a prophylactic for children living under conditions of malnutrition and who are deprived of fresh air and sunlight. Just as rickety children improve under calciferol, similar improvement follows when these children are exposed to direct sunlight or to the artificial ultra-violet rays. Calciferol or food rich in vitamin D will also improve the condition known as osteo alacia from which women often suffer due to repeated pregnancy and lactation and want of proper food, fresh air and sunlight.

Calciferol may be used with benefit during the period of pregnancy and lactation. Children showing defective growth and nutrition and those suffering from caries of the teeth are benefited by its use. Since it helps absorption of

calcium it is necessary that some form of calcium should be given with it

Natural vitamin D as found in fish oils is more potent in facilitating calcification than calciferol, which is chemically related to ergosterol, while natural D factor is related to cholesterol.

Hypervitaminosis.—In moderate doses there is overcalcification at growing ends of the bones and a corresponding diminution of calcium and phosphate in the intestine. In severe poisoning calcium and phosphate may be drawn from bones. Deposits of calcium takes place in the vessels, heart, stomach, colon, kidneys and lungs with formation of calcium phosphate calculi. Toxic symptoms are nausea, vomiting, diarrhoea, loss of weight, malnutrition, fever and nephritis. Spleen and the thymus are atrophied, and the animal loses weight rapidly and dies.

OLEUM UAE

Cod-liver Oil. (Ol. Morrhu.)

Syn.—Oleum Jecoris Aselli.

Syn. I.V.—*Macher tel*, Beng. *Machli ka tel*, Hind

Source.—Obtained from the fresh liver of the cod, *Gadus morrhua*, and other species of *Gadus*, and freed from solid fat by filtration at about 0°C. It contains in 1 gm. not less than 600 Units of vitamin A activity, and not less than 85 Units of antirachitic activity (vitamin D).

Characters.—A pale yellow liquid; odour, slight, but not rancid; taste, bland or slightly fishy. Slightly soluble in alcohol (90 p.c.); miscible with ether, with chloroform, and with light petroleum.

Composition.—The chief constituents are *Vitamins A and D*, also (1) *Jecolein* and *therapin*, the glycerides of unsaturated acids. (2) *Palmitin* 4 p.c. (3) Free *fatty acids* (oleic, palmitic, stearic). (4) Traces of *cholesterol* and *bile acids*. (5) Trace of *iodine*, *bromine*, *sodium*, *calcium*, *potassium*, *iron*, *phosphorus* in organic combinations. (6) Several *alkaloids* such as *morrhaine*, *aselline*. (7) *Resinous matter*. (8) *Colouring matter*.

B.P. Dose.—*Prophylactic* :—15 to 30 ms. or 1 to 2 mls three times daily. *Therapeutic* :—45 to 90 ms. or 3 to 6 mls three times daily.

OFFICIAL PREPARATION

1. **Extractum Malti cum Oleo Morrhuæ.**—Contains about 36 ms. of cod-liver oil in 240 ms. B.P. Dose—60 to 240 ms. or 4 to 16 mls.

NON-OFFICIAL PREPARATIONS

1 **Emulsio Olei Morrhuæ, B.P.C.**—Cod-liver oil 50, acacia powder 125, tragacanth powder 0.6, elixir of saccharin 0.2, chloroform 0.2, water to 100
Dose.— $\frac{1}{4}$ to 1 oz or 8 to 30 mls

2 **Emulsio Olei Morrhuæ Hypophosph.** B.P.C.—Contains 50 p.c. cod-liver oil Being free from sugar is suitable for diabetic patients Dose.— $\frac{1}{4}$ to 1 oz. or 8 to 30 mls

3 **Ostelin**—A glycerin suspension of irradiated ergosterol, contains 5000 International units of vitamin D per mil in easily assimilable form Powerful antirachitic, 4 drops equal to 1 dr. of cod-liver oil Useful in all conditions where cod liver oil is indicated Miscible with water

4 **Sodium Morrhuate**—Sodium salts of the unsaturated fatty acids of cod-liver oil after extraction by ether. Used in *tuberculosis* and *leprosy* Dose—8 to 30 ms or 0.5 to 2 mls of a 3 p.c. solution subcutaneously 2 to 3 times a week until febrile reaction occurs.

PHARMACOLOGY

Externally.--Cod-liver oil is a bland unirritating oil freely absorbed through the skin.

Internally. **Gastro-intestinal tract.**—On account of its fishy, unpleasant smell, many patients cannot retain it, and with some it causes indigestion. In large doses, it may cause diarrhoea, the oil being expelled in the stools. Cod-liver oil is more rapidly absorbed than other oils, fats, butter, *ghee*, etc. It is also better digested, because the free acids it contains facilitate its emulsification and saponification by its admixture with the alkaline secretions of the pancreas, the intestinal glands and bile. Along with the cod-liver oil, other oils and nitrogenous elements of the food are helped in their digestion, and are also better absorbed. But the value of cod-liver oil depends upon the fact that the liver decomposes fats and yields to the blood "unsaturated" fatty acids which are capable of exerting chemical action more markedly. An increase in the amount of these acids tends to disintegrate the tubercle bacillus.

Tissues and metabolism.—Cod-liver oil is not only quickly absorbed and readily assimilated, but enters into permanent combination with the body cells yielding energy to them. It is therefore a **food**; a tablespoonful yielding about 130 calories. Iodine, bromine, phosphorus, etc., perform their share when administration is continued for a long period. But the specific action of cod-liver oil depends upon the unsaturated fatty acids which serve the immediate needs in the production of energy; the saturated acids are stored in the nature of a reserve. It also oxidises readily in the tissues, checks the wastage of other nitrogenous elements and promotes healthy cell formation and increases body weight. The value of cod-liver oil is really due to the presence of vitamins A and D which are essential for the nutrition and growth of young animals, and for correcting improper balance of calcium and phosphorus intake. Moreover the presence of unsaturated fatty acids and vitamin D helps absorption of calcium (*see* page 99). The true vitamin factor is contained in the 1 p.c. of the nonsaponifiable matter contained in the oil.

The superiority of cod-liver oil over other oils depends chiefly upon (1) rapid absorption, (2) quick assimilation, (3) ready oxidation, (4) higher nutritive value, (5) high vitamin content, and (6) its powerful effect on cell-growth and metabolism. Therefore many morbid conditions of the system due to faulty assimilation and defective oxidation are slowly removed by it.

Elimination.—It is mostly absorbed, a little is expelled in the faeces. Some of the acid ingredients escaping through the skin may produce a sort of acne.

THERAPEUTICS

Externally.—If the oil is not retained, or creates indigestion or diarrhoea, inunction is a good method for introducing it into the system. Wasting diseases of children are specially benefited by this method, the only drawback being its objectionable odour.

Internally—It is of signal service in all sorts of chronic wasting disease dependent on malnutrition and malassimilation, especially so in scrofulous disease in its various forms, and phthisis, caries of bones, chronic joint disease, *e.g.* rheumatic or scrofulous arthritis, long-continued suppuration, chronic bronchitis, general debility due to under-feeding, exhaustion, overwork, etc. Convalescence from acute illness, *e.g.* pneumonia, etc., are benefited under its course. As a nourisher and restorer of nerve-cells, it is of great value in old age, debility or exhaustion.

Being rich in vitamins A and D, it is pre-eminently suited for promoting growth and nutrition, and preventing rickets and defective calcification of teeth. As it contains iodine (0.0001 p.c.) its use has been suggested in the treatment of goitre, which is supposed to be due to deficiency of iodine in the food.

Sodium morrhuate has been used as injection in the treatment of tuberculosis and leprosy, and also as a sclerosing agent in the treatment of varicose veins, hydrocele and varicocele. For varicose veins $\frac{1}{2}$ to 1 c.c. of a 5 p.c. solution is injected at each puncture, and a total of 5 c.c. is given spread over a fortnight. For hydrocele the sac is washed out with sterile water after the fluid has been aspirated, and 4 to 5 c.c. of a 5 p.c. solution is injected through the canula, the puncture closed with collodion and the scrotum massaged for a few minutes. A second tapping and injection is necessary, after which the scrotum becomes normal within three months.

Contra-indications.—Indigestion, nausea, vomiting, eructation, diarrhoea, gastric catarrh, high temperature, severe hæmoptysis, contra-indicate its use.

Mode of administration.—It should be commenced with small doses, say 60 ms. and gradually increased to $\frac{1}{2}$ oz. and given after food twice or thrice daily. In the beginning, say for one week, it is a good plan to give only one dose a day preferably after dinner.

Brown oil is superior to pale oil because it contains more fatty acids but its disagreeable smell and taste are a drawback. Children generally can take it better, or soon get accustomed to its taste, but in the majority of cases a pleasant combination becomes necessary. Saponification should be avoided on account of the chemical changes that would occur with the fatty acids contained in the form of glycerides. In fact the great point is to preserve these acids unchan-

ged. Hence, emulsification, as in Emulsio Olei Morrhue, B.P.C. is to be recommended. It can also be given in flexible capsules, mixed with isinglass jelly, or still better with extract of malt. Some patients prefer to take it on milk, coffee, wine or orange juice. A pinch of salt placed on the tongue, a cut lemon sucked, a piece of fresh ginger well chewed, and some of the juice swallowed before and after the dose, effectively remove the nauseous taste in many instances. To help its emulsification as well as to stimulate the pancreatic secretion, purified ether (10 to 20 ms.) is sometimes combined with it.

OLEUM HIPPOGLOSSI, B.P.C. *Syn.* - *Halibut-liver Oil.* - The oil expressed from the liver of halibut (*Hippoglossus hippoglossus*). Contains high concentrations of vitamins A and D. The vitamin A content as measured by the blue unit test is fifty times greater than cod-liver oil, while the vitamin D content is several times greater than that of cod-liver oil, *i.e.* 2000 units per gram. Largely used in place of cod-liver oil and is free from any strong and unpleasant taste. *Two to three drops provide the vitamin equivalent of a teaspoonful of cod-liver oil.*

Dose. .2 to 5 ms. or 0.12 to 0.3 mils.

VITAMIN E

Syn. - Antisterility Vitamin.

It is a fat-soluble vitamin; and Evans has shown that it is necessary for reproduction and that its absence in the food causes death of the products of conception. Although observations were made on female rats, it has recently been reported that administration of wheat germ oil to women with history of sterility conceived, and those with repeated abortion gave birth to normal living children. It is supposed to be one of the factors which hold oestrogen in equilibrium during pregnancy and possibly acts through the intermediary of the anterior pituitary. In the male its absence causes premature degeneration of the spermatogenetic cells and sterility; while in the female its absence causes sterility.

It is present in most animal tissues but not to a high degree and is not present in cod-liver oil. It is found in abundance in the embryos of seeds and green vegetables, chiefly lettuce, alfalfa, peas, oats, corns and wheat-germ oil. It has been isolated in a crystalline form under the name of *Tocopherol* having the formula $C_{55}H_{100}O_2$.

Vitamin K. - "Koagulation" Vitamin. It is a fat-soluble vitamin first found in the liver oils by Dam and Schonheyder necessary for the coagulation of the blood. It plays an important role in the formation of prothrombin and its deficiency prolongs the clotting time. It is found in green leaves of alfalfa, cabbage and spinach; in strawberry and tomato; soya bean and wheat germ.

Its use so far has not yielded any good results in hæmophilia but Dam and Flavind reported its value in the

treatment of obstructive jaundice associated with reduced prothrombin-content of the blood.

Vita in P is a water-soluble crystalline substance of the flavone group called hesperidin, or citrin, and occurs naturally with ascorbic acid, *e.g.* in lemon juice. It is concerned in the maintenance of capillary impermeability, and has been used in hæmorrhagic diseases. Jersild* reports the case of a woman who suffered from Schonlein-Henoch purpura for eight years and whose symptoms completely disappeared with injections of vitamin P. The improvement was maintained even when ascorbic acid was omitted from the diet.

Hesperidin may be used in doses of 1 grm. daily by the mouth.

SUC SU

Sucrose. (Sucros.). $C_{12}H_{22}O_{11}$

Syn.—*Saccharum Purificatum*; Refined Sugar; Cane Sugar.

Syn. I. V — *Misri, Chini*, Beng.

Source.—Obtained from the juice of the *sugar-cane*, or of the *sugar-beet*.

Characters.—Colourless crystals or crystalline masses, or a white powder; no odour; taste, sweet. Readily soluble in water forming a clear, colourless and odourless syrup.

Enters into.—The preparation of all syrups

ACTION AND USES

Sugar is a food, and tends to produce fat and to maintain body-heat and is used in wasting diseases. It is a demulcent and preservative, and may be given in irritant poisoning, but it is mostly used as a basis of various refrigerant beverages and sherbets. In the form of syrup it is added to various pharmaceutical preparations to cover the disagreeable taste of drugs

Part of it is decomposed in the gut with the formation of acid and gas. It delays digestion and favours development of hyperacidity. Sugar is a valuable diuretic and removes oedema. In the blood it produces a transitory hyperæmia by osmosis, and like salts and urea hinders absorption of water from the tubules.

100 c.c. of 50 p.c. solution of sucrose has been used intravenously to reduce intracranial pressure in head injury without producing a subsequent rise or other untoward effects as are observed after injection of sodium chloride and dextrose.

LACT SU

(Lactos.)

Lactose. $C_{12}H_{22}O_{11}, H_2O$

Syn.—*Saccharum Lactis*; Milk Sugar.

Source.—Obtained from the whey of milk.

* Lancet, 1938.

Characters.—A white, crystalline powder; odourless; taste, faintly sweet. *Solubility.*—1 in 7 of cold, more in hot water.

NON-OFFICIAL AND ALLIED PREPARATIONS

1. **Human Milk, Artificial.**—New milk 30, cream $1\frac{3}{4}$, milk sugar $1\frac{1}{8}$, water 18.
2. **Koumiss, Artificial.**—True koumiss as prepared by the Tartars is a fermented mare's milk. Artificial koumiss may be brewed at home from cow's milk by the following process. Dissolve dextrose $\frac{1}{2}$ oz. in water 4 ozs. and yeast 20 grs. in cow's milk 4 ozs. Pour them into a quart bottle, and fill up with milk. Cork and wire it well, and leave it in a cool place with occasional shaking.

Koumiss is an easily assimilable nutritious food and remedy, valuable in the *wasting disease of the lungs*, in which case it can be taken *ad libitum*. It is borne by stomachs which refuse cod-liver oil. It is also very useful in *dyspepsia*, *infantile diarrhoea* and *kidney disease*.

3. **Kephir.**—Is a fermented milk like koumiss, the ferment being a Caucasian mushroom. It can also be made at home by kephir-ferment, adding a fungus which contains yeast and *Bacillus acidi lactici*.

4. **Somatose.**—Desiccated albumoses. Prepared either from milk or meat. Greatly assists *lactation* and when combined with iron as in **Ferro-Somatose**, is useful in *chlorosis* and *anaemia*.

5. **Dried Milk.**—As a food for infants dried milk has almost entirely superseded "humanised milk." It is the residue left after the natural moisture in milk has been evaporated. When required for use boiled water is added to it.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Lactose is a valuable nutrient, and being less sweet than cane sugar is largely used. It greatly increases the flow of urine and is therefore given in cardiac and renal dropsies. It is largely used in humanising cow's milk for infants and because it does not ferment in the stomach it is the best sweetening agent in infantile dyspepsia and irritable conditions of the stomach. It is considered to be a physiological accelerator of labour pains and for this purpose doses of $5\frac{1}{2}$ to 7 drs. may be given dissolved in half a pint of milk. Sterile milk is used in foreign protein therapy intramuscularly (*see* Protein Therapy).

On account of its hardness lactose is used to facilitate the minute subdivision of other drugs, or to dilute potent substances and bring them up to a uniform standard.

DEXTROSUM

(Dextros.)

Dextrose. $C_6H_{12}O_6$

Syn.—Grape Sugar.

Source and characters.—May be prepared from starch by hydrolysis. In white, crystalline or granular powder; odourless; taste, sweet. *Soluble* in less than 1 part of water, in 50 parts of cold alcohol (90 p.c.), in 5 parts of boiling alcohol (90 p.c.).

GLUCOSUM LIQUIDUM

Liquid Glucose. (Glucos. Liq.)

Syn.—Corn Syrup.

Source.—Obtained by the hydrolysis of starch, and consists of a mixture of dextrose, maltose, dextrin and water.

Characters.—A colourless, or almost colourless, very viscous syrup; odourless; taste, sweet. Freely mixes with water forming a clear solution; *partly soluble* in alcohol (90 p.c.).

OFFICIAL PREPARATION

1. *Syrupus Glucosi Liquidi.* *Syn.*—*Syrup of Glucose.*—33.3 p.c.

PHARMACOLOGY AND THERAPEUTICS

Dextrose is rapidly absorbed when administered by the mouth. Given by the rectum or subcutaneously it does not raise the sugar in the blood so easily. Thus Hopkins found that while dextrose given *per os* produced hyperglycæmia in half an hour, it took four and a half hours when 20 gm. (5 dr.) was given subcutaneously. A definite rise of blood-sugar occurs when given as rectal injection with saline. It undergoes oxidation in the body rapidly, but this depends upon the availability of insulin, and in the absence or deficiency of insulin it cannot be utilised.

Given by the mouth it is of great value in nervousness and subnormal health in infancy supposed to be due to shortage of sugar, in asthmatic attacks of children, and malnutrition. By sparing the protein from destruction and assisting the metabolism of fats, dextrose counteracts acidosis or prevents its onset and is used as a preliminary to volatile anæsthesia to replenish the carbohydrate reserve and to avoid acidosis and delayed chloroform poisoning. It is given intravenously to combat severe toxæmias, as for instance in pernicious vomiting of pregnancy, uræmia, eclampsia, etc. A 5 p.c. solution is approximately isotonic and may be used intravenously alone or with normal saline solution to increase the volume of blood in the treatment of shock following operations, collapse of cholera, dehydration, and as a circulatory stimulant in acute infectious fevers. It is more valuable than the ordinary injection of normal saline solution. In cardiac failure it may with advantage be combined with strophanthin. When given with insulin it improves the glycogen reserve of the heart muscle.

Tubes containing glucose solutions for intravenous use are available in the following strengths, *viz.* 12½ p.c., 25 p.c., and 50 p.c., containing 10 to 200 c.c. each. For all practical purposes 200 c.c. of a 25 p.c. solution (5 gm.) is used. A strongly hypertonic solution favours a more rapid interchange between the tissue and the blood, thus helping dilution of toxin, reduction of œdema and a more rapid storage of sugar by the tissues.

By raising the glycogen content it protects the liver from damage in poisoning by cinchophen, chloroform, carbon tetrachloride, arsphenamine, phosphorus and heavy metals.

Dextrose is of great value not only as a food, which is readily absorbed, but also for its protective action on the

liver in cases where it is affected by disease or likely to be in subjects of surgical operation. It is a valuable article of diet in prolonged fever with tissue destruction, *e.g.* enteric fever. It is easily absorbed from the rectum better than any other food, and is therefore largely used in the treatment of **gastric ulcer**, the patients being given 3 to 4 pints daily of saline sugar solutions thus giving the ulcers every chance of healing. It is also a valuable means of preventing hypoglycaemia which may follow an overdose of insulin in the treatment of diabetes. Similarly when given with insulin it is valuable in **ketosis** or **coma of diabetes**.

Intravenous injection of hypertonic glucose (25 p.c. is strongly hypertonic) causes a temporary reduction in the fluid pressure in the tissues by the withdrawal of water, and is used in arterial hypertension, and to **reduce intracranial pressure** in meningitis, fracture of the skull, etc. The solution should be freshly prepared and kept slightly above the body temperature and the injection made very slowly. It is however not always followed by effective clinical improvement, and after a short interval the pressure rises again much above normal. This is due to a reactionary rise in the intracranial pressure which constitutes a serious drawback to this method of treatment. This has been ascribed to an increase in the quantity of hydrolysable carbohydrate in the cerebrospinal fluid which alters its composition and consequently its osmotic pressure.

5 to 10 c.c. of a mixture containing equal parts of dextrose 50 p.c. and sodium chloride solution 30 p.c. used at one injection is considered as the best treatment for **varicose veins**. The solution should be left in contact with the endothelium for at least 5 minutes with a vein occluder, and subsequently strapped with a gauze pad to compress the vein.

Caution.—Large quantities may give rise to nausea, restlessness, tremors, convulsion and coma. It should be given very slowly specially when concentrated solution is used, 4 c.c. per minute. When a large amount is rapidly thrown into the blood it may cause over-stimulation of insulin producing symptoms of hypoglycaemia, or may cause acute dilatation of the heart. It is better to use insulin to prevent this and also to metabolise the large amount of sugar thus introduced. When using intravenously it should not be combined with sodium bicarbonate as it forms a toxic compound. For intramuscular use the solution should not be stronger than 12½ p.c. and not more than 50 c.c. should be given at a time.

LAEVULOSUM

Laevulose. (Laevulos.). $C_6H_{12}O_6$

Syn.—Fructose.

Source.—Prepared from invert sugar, or from honey. Contains laevulose together with small quantities of dextrose and water.

Characters.—A white or cream coloured, hygroscopic, crystalline powder. Odourless; taste, sweet. Freely *soluble* in water.

ACTION AND USES

Lævulose is more sweet than cane sugar and is more easily assimilated. Like other lævorotatory carbohydrates it is utilised by diabetics and has therefore been used without increasing the excretion of sugar. It is largely used in wasting diseases, specially tuberculosis and scrofula, when as much as several ounces are taken daily.

In normal healthy persons all ordinary sugars, glucose, etc., when administered raise the concentration of the blood-sugar, but not lævulose, if the liver is healthy. If therefore there is a definite lesion in the liver, lævulose acts like ordinary sugar, *i.e.* there is a marked increase of blood-sugar. It is therefore used for testing liver function. After a fast of 12 hours a dose of 50 grms. is administered dissolved in 4 to 5 oz. of water, and the blood-sugar is estimated every half hour for two hours. A rise of 0.03 p.c. above the fasting level indicates hepatic disorder.

GELATINUM

Gelatin (Gelat.)

Source—The air-dried product of the action of boiling water on such animal tissues as skin, tendons, ligaments and bones.

Characters.—In translucent, almost colourless, sheets or shreds. A solution in 50 parts of hot water solidifies to a jelly on cooling. Insoluble in alcohol (90 p.c.) and in ether. Tannin precipitates it.

OFFICIAL PREPARATION

1. *Gelatinum Zinci*. *Syn.*—*Unna's Paste*.—Zinc Oxide 15 p.c. Gelatin 15 p.c.

USES

Gelatin is used as a basis for several pharmaceutical preparations such as suppositories, pessaries, bougies, discs, gelatin capsules, and as a coating for pills. It is largely employed in dietary for making jellies, etc.

It is a powerful protein sparer; being able to save from destruction half its weight of protein, or twice as much as is spared by an equal quantity of carbohydrate. One gramme yields about 4.5 calories. It appears that its value as a protein sparer has been exaggerated. As it does not contain cystin and tryptophane it cannot supply the whole protein need of the body. But when given with other foods, specially with milk it forms a valuable food.

Gelatin is used internally chiefly for its hæmostatic effect. Injection into the gluteal region of sterilised solution of gelatin in physiological salt solution (1 to 2 p.c.) promotes the formation of clot and has been advocated for the treatment of aneurism and internal hæmorrhages to increase the

coagulability of blood. Tubes of sterile concentrated saline gelatin solution are prepared for the purpose. Particular care should be taken to see that the solution is absolutely sterile, as several cases of tetanus are on record, specially because some specimens of gelatin contain tetanus spores. The treatment however is unreliable and sometimes dangerous. For its colloidal value it is often used with saline infusions in the treatment of collapse and shock; but as has been pointed out elsewhere (see page 85) it may cause dangerous symptoms of anaphylactoid reaction producing respiratory distress and cardiac dilatation. Since gelatin contains about 25 p. c. of glycine it may be used in myasthenia gravis and muscular dystrophy. (See page 232).

Medicinally it acts as a hæmostatic, due to an admixture of lime, 0.6 p.c. in solution. A 5 p.c. to 10 p.c. solution may be locally used in wounds, epistaxis, etc.

LECITHIN (*Not official*). *Syn*—Ovo lecithin—It is a normal constituent of brain substance and is obtained from yolk of egg. In yellowish wax like substance, insoluble in water.

Dose—By mouth, 3 to 8 grs. or 0.2 to 0.5 gm., hypodermically, $\frac{3}{4}$ to 2 grs. in sterile olive oil.

NON-OFFICIAL PREPARATIONS

1. **Elixir Ovolecthin**, B.P.C.—Contains 1 gr. of ovolecthin in 1 dr. **Dose**—1 to 4 drs. or 1 to 16 mls.

2. **Pilule Ovolecthini**, B.P.C.—Each pill contains $\frac{1}{16}$ grs. lecithin and $\frac{1}{16}$ gr. stychnine hydrochlor. with althæa, liquorice root, gum acacia, alcohol and glycerin. **Dose**—1 to 4 pills.

PHARMACOLOGY AND THERAPEUTICS

Little if any lecithin is absorbed as such, but it is broken up by the pancreatic juice into glycerophosphoric acid, fatty acids, and choline. It is used chiefly for its supposed action in **improving the nutrition** of the nervous system. It is also stated to increase the number of red blood-corpuscles and to raise their hæmoglobin content. It increases body-weight and improves general nutrition.

GROUP XXI

ALTERATIVES IN GOUT

Guaiacum, Colchicum, Cinchophen

GUAIACI RESINA

(Guaiac. Res.)

Guaiacum Resin. (*Not official*)

Source and characters A resin obtained from the wood of *Guaiacum officinale*. In large masses or sometimes in rounded tears, yellowish green to reddish brown; brittle; fracture, vitreous. Thin splinters, transparent. Powder, greyish but becomes green by exposure to light and air. Odour, on warming somewhat aromatic; taste, slightly acid. **Solubility**.—In alcohol, ether, etc.

Composition.—Contains several resin acids (1) α and β *Guaiaconic acids* (70 p.c.) *Guaiacic* and *Guaiaretic acids*, and (2) *Guaiac β resin*.

Dose.—5 to 15 grs. or 0.3 to 1 gm.

NON-OFFICIAL PREPARATIONS

1. **Mistura Guaiaci**.—Guaiacum resin 25 grm., sugar 25 grm., powdered tragacanth 5 grm., cinnamon water *q.s.* to 1000 mls. **Dose**.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.

2. *Tinctura Guaiaci Ammoniata*.—Guaiacum resin 200 grm., oil of nutmeg 3 mls, oil of lemon 2 mls, strong solution of ammonia 75 mls, alcohol (90 p.c.) to 1000 mls *Dose*—30 to 60 ms or 2 to 4 mls

3 *Confectio Guaiaci Co*, B.P.C. *Syn*—*Chelsea Pensioner*—Guaiacum resin 1, rhubarb 2, acid potassium tartrate 7.50, nutmeg 1, sublimed sulphur 14.50, purified honey 74 *Dose*—60 to 120 grs or 4 to 8 grm

ACTION AND USES

Guaiacum is rarely used now, although in the form of Chelsea Pensioner it is still popular in the treatment of chronic rheumatism and gout. It is supposed to be a specific in gout, but is more useful as a prophylactic in the intervals of gouty attacks. The mixture is more popular than the tincture.

COLCHICUS

Colchicum Corm (Colch. Corm)

Source.—The fresh corm of *Colchicum autumnale*, collected in early summer; or the same stripped of its coats, sliced transversely and dried at a temperature not exceeding 65°C.

Characters.—*Fresh corm*—35 mm. long, 25 mm. broad, conical, hollowed on one side where it has a new corm in process of development, rounded on the other; outer coat thin, brown, membranous; inner coat, reddish-yellow. Internally white, solid, yielding bitter disagreeable whitish turbid juice. *Dried slices*—2 to 5 mm. thick, yellowish at circumference, reniform, firm, whitish, amylaceous. Taste, bitter. No odour.

Composition.—(1) *Colchicine*, 0.4 p.c. an active alkaloid. (2) *Starch*, gum, sugar, tannin, etc.

Incompatibles.—Astringents, tincture of iodine, and guaiacum.

B.P. Dose—2 to 5 grs. or 0.12 to 0.3 grm.

OFFICIAL PREPARATION

1. *Extractum Colchici Siccum*.—Contains 1 p.c. colchicine, or $\frac{1}{10}$ gr. in 1 gr. *B.P. Dose*.— $\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.

COLCHICUS

Colchicum Seed. (Colch. Sem.)

Source.—The dried ripe seeds of *Colchicum autumnale*.

Characters.—2 to 3 mm. in diameter, subglobular, slightly pointed, rough, reddish-brown, hard, tough, minutely pitted. Endosperm oily. Taste, bitter. No odour.

Composition.—(1) *Colchicine* 0.3 to 0.6 p.c. (2) A fixed oil.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

OFFICIAL PREPARATIONS

1. *Extractum Colchici Liquidum*. *Syn*.—*Fluid Extract of Colchicum*.—Contains 0.3 p.c. w/v of colchicine, or $\frac{1}{10}$ gr. in 5 ms. *B.P. Dose*.—2 to 5 ms. or 0.12 to 0.3 mil.

2. *Tinctura Colchici*.—0.03 p.c. w/v of colchicine, or $\frac{1}{10}$ gr. in 15 ms. *B.P. Dose*.—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATIONS

1 *Colchicina*, U.S.P.—Pale yellow, amorphous scales, or powder. *Dose*, U.S.P.— $\frac{1}{100}$ gr or 0.0005 grm.

2. *Colchicine Salicylate*—A yellow powder, soluble in water. *Dose*— $\frac{1}{120}$ to $\frac{1}{80}$ gr or 0.0005 to 0.002 gr

PHARMACOLOGY

Externally.—Locally applied to the skin and mucous membrane colchicum acts as an irritant, producing redness

and smarting. Inhaled, its powder causes sneezing and watering of the eyes.

Internally. **Gastro-intestinal tract.**—(Given by the mouth or injected hypodermically colchicine increases the gastric and the intestinal secretion, but this effect is not observed in every case. In moderate doses it causes purging, vomiting and abdominal pain. In large doses it is a powerful gastro-intestinal irritant. These symptoms appear several hours after administration even if the dose is large. This is probably due to the conversion into oxydicolchicine. According to Dixon colchicine acts on the intestine in the same way as pilocarpine and is antagonised by atropine. This however does not explain the whole action, *e.g.* acute inflammatory reactions, which are really due to the irritant action of the drug on the mucous membrane, or as Fuehner and Rehbein have pointed out being due to capillary vasodilatation produced by the drug either directly or through excretion.

Nervous system.—Its action here resembles those of heavy metals or some bacterial poison, some however attribute them to collapse resulting from severe irritant action on the alimentary tract. Later there is both motor and sensory paralysis, and death takes place from respiratory and vaso-motor paralysis.

Circulation and respiration.—It depresses the circulation, lowers the blood-pressure and slows the respiration. The pulse becomes feeble, soft and rapid. These effects are probably due not so much to the colchicine acting on the cardiac and respiratory organs, as to the consequences of severe gastro-enteritis.

Kidneys.—Its action on the kidneys is uncertain. In some there is anuria, in others there is an increase of urine. The urinary constituents are not affected.

Acute toxic action.—The chief symptoms are those of gastro-intestinal irritation in a grave form. Violent burning in the throat, oesophagus and stomach; intense thirst; severe colic with vomiting and purging; the stools being first serous, then slimy and finally bloody; great prostration, rapid, feeble and thready pulse; cold skin bedewed with sweat; slow and laboured respiration and lastly death during collapse from respiratory paralysis; consciousness not being lost.

Treatment. Emetics, followed by demulcent drinks, as white of egg freely diluted with water. Tannic acid is a chemical antidote. Stimulants, tea, and coffee; morphine hypodermically.

Chronic toxic action.—Small medicinal doses long continued, bring about furred tongue, disagreeable taste, loss of appetite, thirst epigastric pain, flatulence, and diarrhoea.

THERAPEUTICS

Internally.—Striking results follow administration of colchicum in acute gout. The severest pain and inflammation are removed in a few hours after 15 to 30 ms. of the tincture of colchicum. It succeeds well in first attacks on

robust patients, but cannot prevent a relapse even if it is continued during the interval between the attacks. How it acts in this disease is not known. Garrod has experimentally shown that colchicum can in no way influence the elimination of uric acid in gouty people. Besides its specific property in gout, colchicum is useful in many other complaints of gouty people, such as dyspepsia, headache, hepatic congestion, neuralgia, etc. It affords no relief in the chronic gout of old debilitated persons. Rheumatism is never benefited.

Caution.—It should be avoided or given with great caution to the weak, the infirm, and those who suffer from cardiac weakness, chronic diarrhœa, chronic dysentery or colic

Prescribing hints—Colchium may be administered in *acute gout* in two ways—either in full doses, say 20 to 30 ms. of the tincture, repeated every 2, 3 or 4 hours, or in repeated small doses, say 10 ms. of the tincture, every 3, 4 or 6 hours while the pain lasts. It should never be combined with acids as they *intensify* its irritating property, while alkalies given with it mitigate the same. Ordinarily the tincture is used, but it should be noted that the tincture of the seeds is stronger than that of the corm. As it is a cardiac depressant, the bowels must always be kept open during a course of colchicum to prevent accumulation of the drug in the system.

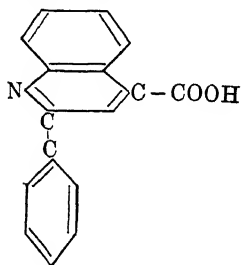
CINC HENU

(Cinchophen.)

Cinchophen

Syn.—Quinophan; Atophan; Agotan

Source.—It is 2 phenylquinoline-4-carboxylic acid. Prepared by the interaction of pyruvic acid and benzylideneaniline. Contains not less than 90 p.c. $C_{16}H_{11}O_2N$.



Characters.—White, or yellowish, powder or crystals; almost odourless; taste, slightly bitter. *Insoluble* in water, soluble in about 120 parts of alcohol (95 p.c.) in 100 parts of ether, and in solutions of alkali hydroxides, carbonates and bicarbonates.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 gm.

NON-OFFICIAL PREPARATION

1 **Neocinchophenum, USP.**—Ethyl ester of 6-methyl-2-phenylquinolin-4-carboxylic acid. Pale yellow, crystalline powder. Odorless and tasteless. Nearly insoluble in water. Soluble in hot alcohol and very soluble in ether and in chloroform. *Dose, USP*—8 gr. or 0.5 gm

PHARMACOLOGY AND THERAPEUTICS

Its action resembles the salicylates, and it is a valuable *antipyretic*, *analgesic* and *antirheumatic*. It reduces temperature by causing vaso-dilatation and diaphoresis.

In therapeutic doses, even on a purin free diet, it increases the **elimination of urates and uric acid** and causes a fall in the uric acid content of the blood. It does not interfere with the uric acid formation excepting eliminating it in increasing amount. This effect continues as long as the drug is used. It has been suggested that it increases uric acid elimination either by increasing the permeability of the kidneys to uric acid or by hindering the normal reabsorption of urates by the tubules. To prevent precipitation of urates, the urine should be kept alkaline by the administration of bicarbonate, acetate or citrate of potassium and sodium.

It is eliminated within 3 to 6 hours after ingestion.

Cinchophen is largely used in **rheumatism** and **gout**. In acute rheumatic fever it is given in 10 gr. doses 3 or 4 times a day. Such large doses do not cause nausea or irritation of the kidneys and are better tolerated when given with alkalies. In gout its effects are more marked in acute attacks, relieving both pain and swelling rapidly. The usual dose is 8 gr. three or four times a day.

For its analgesic effect it is used in sciatica, headaches and neuralgias.

As a rule no untoward effects are noticed even when used in large doses. But attention has been drawn recently to cases of poisoning following the use of cinchophen. In many cases the symptoms point to special idiosyncrasy to the drug. The symptoms are those of cinchonism, cutaneous rashes, gastro-intestinal and hepatic disorders. Occasionally *vertigo*, *jaundice*, *digestive trouble*, *anorexia*, *fever* and *urticarial eruptions* may appear. Cases of acute yellow atrophy of the liver have been recorded due either to individual susceptibility or uninterrupted use for prolonged periods. Albuminuria or any kind of nephritis should be regarded as contra-indication. Disturbed kidney function possibly retards excretion of the drug, but impairment of the liver function renders the patient more susceptible to the drug. If there is nausea or impairment of appetite its use should be withheld.

It should be taken *after meals* followed by a draught of water. Because of the danger of accumulation, the treatment should not be continuous, but should have periods of rest.

Neocinchophen is tasteless and does not cause gastric irritation. It is considered much safer to the liver than cinchophen. It is however less analgesic.

Toxic symptoms. Severe jaundice with tender enlarged liver, definite hemorrhagic rash, bilirubin and albumin in the urine, with pale stool without any bile were observed in a man who had 118

grammes in 41 days for chronic rheumatism. Coagulation time of the blood was increased (7 minutes), bleeding time was normal. During the illness nitrogen excretion was high (15 to 18 grammes daily) showing breakdown of tissue protein. Death from subacute yellow atrophy of the liver after 37½ grs. in five days have been reported by Fraser.* Toxic symptoms have been observed after doses ranging from 54 grs. in five weeks to 7,200 grs. in four months.

Treatment.—Stoppage of the drug and administration of dextrose 60 grm. with 20 units of insulin twice a day followed by duodenal lavage and administration of magnesium sulphate.†

GROUP XXII

DRUGS ACTING ON METABOLISM

Metabolism is the sum total of the chemical exchanges taking place in the tissues through the medium of the blood. These exchanges represent two phases, *viz* *anabolic* and *katabolic*. The changes by which the different food materials are utilised in the building of the body represent the anabolic or constructive phase; whereas the breaking down process by which the waste products are produced with liberation of heat and energy represent the katabolic phase. The products of metabolism are CO₂, urea, water, sulphate, etc., and these are excreted by the lungs, with urine, fæces and sweat. The oxygen taken up by the lungs plays a most important part and the physiological oxidation of the body cannot be separated from the general metabolic phenomena.

Metabolism therefore embraces all changes taking place in the body, and the most important factors concerned in the regulation of metabolism are food, exercise, light and air. Normally the anabolic and katabolic processes are more or less balanced; the income in food being balanced by the expenditure of carbon, nitrogen and water in the urine, stool, sweat and respiration.

The term *basal metabolism* is used to denote the amount of potential energy or heat required to maintain the heat of the body, activity of the heart, respiratory movements, etc., when in complete rest. It is the smallest energy output compatible with health. Basal metabolism is in proportion to the surface of the skin, and since a tall person has a larger skin area, he requires more heat and therefore more food to keep the temperature normal.

Since the body is undergoing constant changes, the elements which go to build and maintain the body must perforce be subject to similar changes. Food is therefore necessary for growth and to replace the wear and tear of the body. The proteins contribute to the formation and repair of tissues, regulate the absorption and utilisation of oxygen, and play an important part in the chemistry of

**British Medical Journal*, 29th December, 1934

†*British Medical Journal*, Nov. 14, 1931. *Epitome*.

nutrition. They are characterised by the presence of nitrogen. If the income of nitrogen received from the protein food is equal to the amount of nitrogen eliminated with the different excreta, the body is then said to be in nitrogen equilibrium. If less is eliminated, it implies that the body is storing protein, whereas if more is excreted then the body is losing protein. During the growing period and convalescence, less nitrogen is eliminated to enable the body to build up tissue. Under normal conditions our diet is so regulated that the nitrogen equilibrium is maintained at a constant level. Proteins stimulate metabolism and the specific dynamic action is the result of deamination of the amino-acid, glycine, etc.

Carbohydrates and fats play the same role in the body, being sources of heat and energy. Fat however may be stored up in the tissue as part of body fat, or may be synthesised with other substances to form more complex constituents of the body, *viz.* lipoids. Carbohydrate is oxidised in the body to supply the necessary heat and is stored up as glycogen in the liver and muscles to be doled out as sugar according to the requirements of the body for use in tissue metabolism. This important function may be disorganised through various causes, *viz.* injury to the central nervous system, and over secretion of the adrenals or hypophysis, and is regulated by the internal secretion of the pancreas.

The role of vitamins in the general metabolism is now widely recognised and diseases like rickets, beri-beri, scurvy and pellagra are regarded as the result of metabolic disturbances caused by deficiency of certain vitamins in the food.

Inorganic metabolism.—Since most of the therapeutic measures depend for their action on the alteration they produce in the inorganic constituents of the body, a knowledge of the metabolism of the inorganic salts is a great help to the pharmacologist. Mineral salts form about one-twenty-fifth part of the whole body. The chief mineral elements are calcium, sodium, potassium, magnesium, iron, manganese, zinc, copper, lithium and barium; phosphorus, sulphur, chlorine, silicon, fluorine, etc. Of these calcium, sodium, potassium, manganese, iron and copper are the most important and are the alkali forming elements; while phosphorus, sulphur and chlorine are the acid forming ones. These salts form an essential part in the composition of living matter and maintain a normal composition and osmotic pressure in fluids and tissues of the body and play an important part in the regulation of the acid-alkali balance. Sodium chloride occurs in all the tissues and fluids of the body. Since every cell contains phosphorus, it is essential for the multiplication of cells and growth of the body. The phosphates of sodium and potassium regulate the reaction of body fluids and tissues, control the osmotic pressure

and inter-change of fluids. Calcium phosphate is essential for the development of bones, and calcium itself performs many important functions already discussed (see p. 97). Calcium metabolism is intimately related to vitamin D, parathyroid and thyroid, also on the reaction of the blood; acidosis helps retention of ionised calcium, while alkalosis decreases the amount of diffusible calcium and produces tetany. Iron is an important element of hæmoglobin. It is also present in minute quantities in the muscles and other tissues where it helps the oxidation and catalysis of enzymes. Iodine is stored up as thyroxine in the thyroid gland and deficiency of iodine results in goitre.

Within recent years the effects of light and air on metabolism have received much attention owing to the admirable work of Sir Leonard Hill. He has shown that under cool open air condition the tone of the body is much increased, and the growth of infants becomes more rapid in the cool months. Exposure of the body to the cool atmosphere has a stimulating effect on the general metabolism, whereas heat has a depressing effect with a lower basal metabolism. A sufficiency of sunlight with cool, dry and moving air is conducive to health and gives a feeling of well-being. Light and air exert a much more important effect on the body metabolism. The ultra-violet rays of the sunlight are absorbed by the skin and form vitamin D so important for the formation of bony skeleton and prevention of rickets. Similarly exercise by throwing more work on the muscle increases protoplasmic activity which implies supply of more nutrient material and oxygen.

T Y R I EU

Thyroid. (Thyroid)

Syn.—Thyroideum Siccum; Thyroid Extract; Desiccated Thyroid Gland

Source.—Prepared from the thyroid gland of oxen, sheep, or pigs. Remove the connective tissue and external fat from the glands; dry at temperature not exceeding 60° C; powder; remove all fat by extraction with light petroleum, dry. Contains 0.1 p.c. of iodine in combination as thyroxine.

Characters.—A cream-coloured amorphous powder. Odour and taste, faint and meatlike.

Storage.—Thyroid should be kept in well-closed container, and stored in a cool place.

B.P. Dose.— $\frac{1}{2}$ to 5 grs. or 0.03 to 0.3 gm.

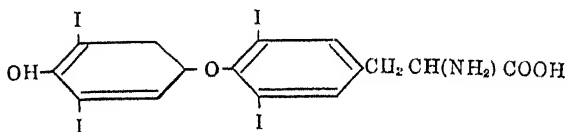
T Y X I N S I U

(Thyroxinsod.)

Thyroxine-sodium. $C_{15}H_{10}O_4NI_4Na$

Source.—Prepared by the action of the limited amount of sodium carbonate upon thyroxine, obtained by the controlled hydrolysis of thyroid gland with barium hydroxide and subsequent purification, or

by synthesis. Contains not less than 61 p.c. and not more than 66 p.c. of iodine.



Characters.—A white, crystalline powder. Sparingly *soluble* in cold water, freely in solution of sodium carbonate or hydroxide. Unstable in alkaline solution.

N.B. It should be dispensed when thyroxine is ordered.

B.P. Dose.— $\frac{1}{10}$ to $\frac{1}{4}$ gr. or 0.0001 to 0.001 grm.

PHARMACOLOGY

Thyroxine is a powerful poison. When thyroxine or thyroid extract is administered to normal persons no obvious effects are observed unless it is pushed to elicit toxic symptoms. The effects observed are quickening of the pulse, vomiting and diarrhoea, increased metabolism, particularly an increase of nitrogenous metabolism, loss of weight and emaciation. A single dose has very little effect, but small repeated doses produce toxic symptoms. In fact a single large dose even when administered intravenously does not produce any effect for 24 to 36 hours. Continued use tends to produce cumulative effects.

Internally. Circulation.—Given by the mouth for a prolonged period, thyroid causes increase in the pulse-rate, palpitation and weakness of the heart-beat. Sometimes no acceleration is observed even after its use for a long time. This is possibly due either to deterioration or to absence of thyroxine from the dried gland. The cause of acceleration is not clearly understood, and may be due to stimulation of the sympathetic or to increased metabolism. Thyroid extract injected into the body causes a fall of blood-pressure, due, according to Dixon, to the presence of organic extractives. Given by the mouth it has no effect in reducing the blood-pressure. It increases the number of lymphocytes in the blood.

Metabolism.—Thyroid increases metabolism of the proteins, fats and carbohydrates even in normal animals, although it is more marked when it is low as in thyroid deficiency. The excretion of nitrogen and carbonic acid, and the consumption of oxygen, are increased, so that an excess of urea, uric acid and xanthin bases is eliminated through the kidneys and more carbonic acid by the lungs. In fact more nitrogen is excreted than is taken by the food, which implies that the excess is due to destruction of tissue protein, and since the glycogenic function of the liver is disorganised, the use of carbohydrate or fat does not check the protein destruction. It also influences the calcium metabolism and helps removal of calcium (together with phosphorus)

from the bones thus making them rarefied (osteoporosis), but there is no increase of serum calcium as happens with parathormone, and there is increased excretion in the urine and fæces. Its mode of action on calcium metabolism is not known. As a result of all these effects the body temperature rises, and although the appetite improves the weight falls which is greater than can be accounted for by the loss of tissue protein. Cushny suggests that the most important factor in the reduction of weight is diuresis, which helps to eliminate a large amount of fluid not only in subjects of myxœdema but also in persons suffering from obesity.

The basal metabolism is increased about 2 p.c. by 1 mg. of thyroxine in adults weighing 150 pounds, due to increase of fat and carbohydrate metabolism. In myxœdemic patients 10 mg. may produce an increase of 30 p.c. The results are the same whether thyroxine is given by the mouth or intravenously. If it is continued in large doses, symptoms of hyperthyroidism become marked by the 5th or 6th day.

The normal human thyroid contains about 10 to 15 mg. of iodine, but this depends upon the quantity of iodine taken with food. When iodides are given this iodine is doubled. The gland is concerned in the development and maintenance of the normal functions of the body, and this it does by virtue of its internal secretion, which can only be formed when there is a certain amount of iodine in the food. It is possible that part of its activity is dependent upon the supply of adrenaline, and through its effect on the autonomic nervous system it increases the tone of the uterus and intestine (Bastedo). According to Bircher thyroid promotes the growth of bone in normal animals and for this reason has been used to promote union of bones in delayed healing of fractures.

Kidneys.—Thyroid is a powerful diuretic, but the exact manner of its action is not clear. The increased excretion of urea is partly responsible for the effect, although some attribute a specific action on the kidney. It is possible that the passage of a large amount of water and sodium chloride to the circulation produces hydræmia of the blood with consequent diuresis.

Nervous system.—Large doses sometimes cause tremors, restlessness and insomnia; and mania has been known to follow its use for the cure of obesity.

Excretion.—It is chiefly excreted by the kidneys, and when continued long may cause gastro-intestinal disturbances and diarrhœa.

Acute Thyroidism.—The symptoms produced by an overdose are as follows:—Rapid pulse, fever, headache, tendency to syncope, sickness, diarrhœa, restlessness, wandering pains, pruritus, and rarely delirium.

Chronic Thyroidism.—The symptoms are:—Loss of weight, muscular weakness and paresis, falling out of the hair, protrusion of the

eyeballs, dilatation of the pupils with widening of the palpebral fissure, and finally death from malnutrition and asthenia. It will be noted that these symptoms closely resemble those of exophthalmic goitre.

THERAPEUTICS

The chief use of thyroid is in the treatment of myxœdema which is a disease due to atrophy of the thyroid gland. In six weeks all symptoms will probably have disappeared, but to prevent recurrence the patient must take it twice a week for the rest of his life. In the same way it is invaluable in cretinism, which is a form of idiocy associated with dwarf-growth, due to congenital absence of the thyroid ($\frac{1}{320}$ to $\frac{1}{160}$ gr. thyroxin-sodium daily or on alternate days). Under this treatment, however, the bones of cretins have a strange tendency to bend. Thyroid has also proved of benefit in congenital imbecility, the insanity of the menopause and in menopausal headache, specially when associated with sub-normal metabolic rate.

Paradoxical as it may appear thyroid is useful in goitre. In this condition the enlargement of the gland does not mean increased secretion, on the other hand the gland hypertrophies to compensate for the deficiency of the thyroxine. But it is useless in exophthalmic goitre. As thyroid hormone stimulates metabolism, it has been used in diverse conditions. For instance, remarkable results may be obtained in certain diseases of the skin, specially psoriasis, pityriasis rubra, ichthyosis, eczema, lupus, etc., whilst it sometimes causes a luxuriant growth of hair in alopecia. Administered with calcium it is of great value in chilblains.

In obesity thyroid treatment has been found to be of value, but may do harm if used without proper precaution. It sometimes reduces the weight to a great extent, but the effect should be regarded as the toxic effect and is often followed by symptoms of hyperthyroidism. Small doses of thyroid form a valuable remedy in obstinate constipation so often present in slight forms of hypothyroidism.

Thyroid deficiency is to a large extent responsible for a number of complaints and infections, and its administration has been advocated in acute and chronic arthritis, angina minor, acute tonsillitis, phlegmasia alba dolens, *B. coli* infection and chronic gout.

As a diuretic it is said to be valuable in reducing œdema of Bright's disease.

Cheron used it as a galactagogue, and in threatened abortion. Different observers have reported benefit from its use in infantile wasting, ununited fracture, and in assisting the development of backward children.

It is worthy of trial in children who fail to grow, in nocturnal enuresis, night terrors, and in those who suffer from

relaxation of the ligaments causing knock knee, painful heel, flat foot or lordosis.

Prescribing hints.—Thyroid is best administered in the form of powder or as tablets. It is not as a rule a dangerous remedy, but when it is continued for a prolonged period it should be used with care, specially if the heart is affected. It is now realised that large doses are not required. A total daily dose of 6 grs. of the extract of fresh gland seldom needs to be exceeded, and it is wise to start with $\frac{1}{2}$ gr. doses three times a day. It should be noted that the extract of the desiccated gland is five times as strong as the fresh gland. Thyroxine can be given by the mouth, but it acts better when given intravenously.

Thyroxine-sodium is used under the same conditions as thyroid; and it should be used when thyroxine is ordered. The usual method is the intravenous route, and although it may be given by the mouth, its absorption by this route is uncertain. In every case the optimal dose should be first determined, the exact determination of which depends upon the basal metabolic rate. Ordinarily $\frac{1}{30}$ gr. daily in normal adult will produce symptoms of hyperthyroidism. Cases of myxedema require from $\frac{1}{40}$ to $\frac{1}{30}$ gr. (0.0015 to 0.002 gm.) of thyroxine-sodium daily.

Contra-indications.—Hypersecretion of the thyroid, and when there are toxic symptoms from hyperthyroidism. Sleeplessness, delirium, cerebral excitement and when the heart is rapid or irritable. In acute inflammatory condition of the skin and progressive loss of weight.

LIQUID PARATHYROID, U.S.P.

(Liq. Parathyroid)

Solution of Parathyroid. (Not official)

Syn—Parathyroid Extract; Parathormone.

Source—Obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man.

One c.c. possesses a potency equivalent to not less than 80 parathyroid units and not more than 120 parathyroid units, each unit represents $\frac{1}{100}$ th of the amount required to raise the calcium level of 100 c.c. of the blood serum of normal dogs 0.001 gm., within from 16 to 18 hours after administration.

Dose, U.S.P.—25 units by hypodermic injection.

PREPARATION

1. **Desiccated Parathyroid Gland.**—**Dose.**— $\frac{1}{100}$ to $\frac{1}{10}$ gr. or 0.003 to 0.006 gm. by mouth. Probably it is inert.

PHARMACOLOGY AND THERAPEUTICS

Parathyroids regulate the calcium metabolism, and increase the ionisable calcium content of the blood, and detoxicate certain metabolic poisons. Administration of parathormone (Collip) regulates the concentration of calcium in the body which has a sedative effect on the nervous system. The removal of the glands is followed by a condition known as tetany which is characterised by increased

excitability of the motor nerves and certain parts of the central nervous system. Serum calcium falls from 10 to 5 or 6 mg. and the symptoms of tetany are due to the decrease of serum calcium. Administration of parathyroid raises the serum calcium, and since the absorption of calcium is not increased, nor its excretion diminished but rather increased (this occurs even after complete removal of the alimentary canal), the rise of serum calcium is attributed to the mobilisation of calcium from the soft tissues and bones. In fact after its use the bones become softer, and in growing animals and after fracture less calcium is deposited.

Apart from raising the calcium in the blood it increases the excretion of phosphorus in the urine. If however it is continued long in large doses, after the blood calcium has reached a certain height, the effect is reversed and the blood phosphorus rises again.

A single large dose has little effect, but repeated smaller doses show symptoms of hypercalcemia by raising the calcium content of the serum to over 12 mg. or even up to 20 mg. per 100 c.c. Its administration is followed by vagotonia with slow pulse, hyperemia of the abdominal organs and increased gastric and intestinal movements. Kidneys show marked congestion, specially in the glomeruli, and its administration is followed by **diuresis**. Its use has therefore been advocated in oliguria and anuria associated with glomerulo-nephritis, specially when the blood calcium is lowered. In **tetany** the calcium content of the blood is reduced, and the administration of the extract increases the calcium and relieves the symptoms more effectively than the use of calcium salts alone. It has also been used in other spasmodic diseases like paralysis agitans, eclampsia, etc., but without much success. Its use has been advocated in sprue with simultaneous use of calcium.

In lead poisoning it is useful after the subsidence of acute symptoms as it helps liberation of lead with calcium. But large doses are required to produce this effect.

It has been extolled by Grove and Vines in the treatment of varicose ulcers of the leg and also in gastric and duodenal ulcers. They found a deficiency of ionic calcium in the blood which was restored to normal by the use of parathyroid accompanied by the healing of the local lesion and general improvement of the health. This however has not been supported by other observers.

Except in cases where there is distinct deficiency of blood calcium, *i.e.* below 10 mg. per 100 c. c. its use in other conditions is at best a speculative one. As it mobilises the calcium from other tissues, mainly the bones and muscles to the blood, its use is contraindicated in those conditions in which the object is to bring about deposition of calcium

in the bones and not merely to raise the serum calcium, e.g. in rickets, osteomalacia, etc.

The best results are obtained when the extract is administered subcutaneously as in the treatment of tetany. It has been given by the mouth but the results have not been very satisfactory, and it is doubtful whether given by the mouth it raises the calcium content of the blood. The administration of the extract should be controlled by determination of the calcium content of the blood to avoid hypercalcaemia.

Toxic symptoms.—Parathyroid is a powerful drug and is cumulative, and repeated smaller doses show symptoms of hypercalcaemia by raising the calcium content of the serum to over 12 mg. or even 20 mg. per 100 c.c. The symptoms of hypercalcaemia are restlessness, muscular weakness, vomiting, loss of appetite, diarrhoea, impaired circulation, dullness, drowsiness, hæmaturia, collapse and death

INSULIN

Insulin. (Insulin.)

Source.—A preparation containing the specific antidiabetic principle of the mammalian pancreas. Prepared in the form of powder or solution. May be obtained in solution by dissolving the necessary quantity of dry powder in distilled water acidified to a reaction between the limits of pH 3 and pH 4, so that the solution contains 20 units per mil. Some antiseptic is added to prevent growth of bacteria

Characters.—Colourless liquid, free from turbidity and from matter which deposits on standing.

May be obtained in tablet form which must be readily and completely soluble in water.

Storage.—It should be kept at as low a temperature as possible above its freezing point, and should not be exposed to temperature above 20°C when it will retain its potency for at least 18 months at reaction between pH 3 and pH 4

The label should state (1) date of manufacture; (2) date after which it should not be used.

B. P. Dose—5 to 100 units (subcutaneously).

Three units of insulin is the amount in c.c. which on subcutaneous injection into a normal rabbit weighing 2 kg. reduces its blood-sugar from the normal of 0.15 p.c. to 0.045 p.c. within 2 hours. At this point the rabbit develops coma and convulsion.

ACTION AND USES

Insulin is the active principle of the pancreas, which is produced in the islets of Langerhans, and which being constantly secreted into the blood plays an important part in the metabolism of carbohydrate.

Removal of pancreas in animals is followed by a rise of blood-sugar above normal and appearance of sugar in the form of dextrose in the urine. Since the glycosuria appears even in the absence of any carbohydrate food from conversion of other substances in the body into dextrose, the body gets depleted of sugar and the animal loses weight. There is not only failure to utilise sugar, but the metabolism of

fats is also affected, and as a result of incomplete oxidation of fats there accumulates in the body *aceto-acetic acid* and *β -hydroxybutyric acid* which are excreted in the urine. An injection of insulin controls carbohydrate metabolism, and will reduce blood-sugar of healthy animals from the normal of 0.12 p.c. This effect takes place normally within an hour of its administration and is maintained several hours, but rarely over ten hours. The extent of the fall depends upon the amount given, and an overdose produces symptoms of hypoglycaemia.

It helps the tissues to metabolise sugar and enables the liver and muscles to store glycogen and to utilise glucose as a source of energy. This improved combustion of sugar helps combustion of fats and corrects faulty metabolism thereby helping disappearance of ketone bodies and acidosis responsible for diabetic coma. Since injection of insulin in depancreatized dog, which is also given sugar, increases the respiratory quotient, it is evident that sugar is being oxidised, and it has therefore been suggested that insulin supplies the missing link, and by the control it exerts on the glycogenolytic ferment permits of sugar being converted into a form suitable for oxidation. Insulin therefore has been extolled as a most valuable drug in the treatment of **diabetes**. Under its use there is a marked reduction of the blood-sugar which remains at the normal level while the glycosuria disappears altogether. Along with the disappearance of sugar from the urine the ketone bodies usually disappear from the urine and blood within twenty-four to forty-eight hours, showing that fats are more efficiently dealt with. The carbohydrates are utilised more freely with a rise of respiratory quotient. In fact patients under insulin treatment show clear signs of improvement, and the cardinal symptoms of diabetes are relieved.

The best results are obtained in cases of threatened or actual **diabetic coma**, when larger doses (40 to 60 units) are given preferably by the intravenous route and as much as 200 units may be given in 24 hours. Since acidosis is the result of imperfect combustion of fats, it is necessary that fats should be withdrawn and carbohydrates in the shape of glucose administered. Other measures such as rectal injection of 3 p.c. solution of sodium bicarbonate should be adopted. To be successful the treatment must be started early. A case in which the coma has existed for more than twenty hours without any improvement is hardly likely to recover under insulin. When large doses of insulin are administered glucose should also be given with it to prevent hypoglycaemia.

It has been used with success in the treatment of furunculosis not only when associated with diabetes but also in cases where there is no sugar in the urine but the blood-sugar

content is high. Carbuncles in diabetics heal more rapidly under insulin treatment. Conditions depending on hyperglycæmia, *e.g.* neuralgia, pruritus, balanitis, etc., disappear under insulin. It is also of great value in acidosis and ketosis of non-diabetic origin. Thus hyperemesis gravidarum is successfully treated with injection of insulin and glucose. Similarly cyclical vomiting of children is equally benefited by insulin and glucose. Its use has been suggested in exophthalmic goitre, it improves the goitre and exophthalmos and reduces the basal metabolic rate. As a prophylactic against acidosis prior to surgical operations and anæsthesia, specially in the diabetic, its value is undisputed.

Its use has been suggested in **malnutrition**, it increases the weight in patients with intact carbohydrate metabolism, improves the subcutaneous tissue and gives a healthier appearance to the skin. The method is to give 10 units three times before each meal the first day, and increasing by 5 units daily up to 20 to 30 units. It has been suggested that the good effects are due to (1) an increased demand for food; (2) an improvement in the nutritive condition, causing an increased desire to eat; and (3) training of the insulin-producing organs by carbohydrate administration to produce more insulin.

Insulin has been used in the treatment of **drug addiction**, *e.g.* during the withdrawal stage of morphine and in mental diseases of both diabetics and non-diabetics (schizophrenics). In mental cases it is given in large doses to induce shock.

Methods of Administration.—Insulin has no action when given by the mouth or per rectum, as it is rapidly destroyed by the digestive enzymes. Within certain limits perilingual administration may be successful, but cannot be regarded as a substitute for injection, although Mukherjee* claims that the phosphotungstate precipitate is active by the mouth. It is doubtful, however, whether its absorption is sufficient to replace subcutaneous injection, and in all cases where immediate effect is necessary it should always be given subcutaneously, or in urgent cases, intravenously. Two perilingual tablets can only be given daily which means ten units of insulin. One unit of insulin will metabolise 2 grms. of carbohydrate and 30 to 40 units a day is the normal dose in severe cases. The usual dose for an adult is 10 units, repeated twice daily, and should be given a quarter to half an hour before a meal so that it can exert its effects on the glucose which reaches the blood from the meal. This precaution will prevent the risk of hypoglycæmia. The dose of insulin depends upon

- (1) the severity of the case;
- (2) weight, a heavier individual requires a larger dose;

* Journal of Physiology, 1935. p. 362.

- (3) amount of intake of food; and
- (4) septic or other complications.

Whenever possible the treatment should be controlled by blood-sugar estimation. If this is not practicable the dose of 20 units should not be exceeded. During insulin treatment the patient should not be allowed to fast too long after the injection. When the insulin requirement exceeds 40 to 50 units daily, it is better to divide it into two or three doses. The single dose method is unsatisfactory when the daily requirement exceeds ten units.

Before adopting treatment always make sure that the case is really one of diabetes. It is dangerous to treat cases like renal glycosuria where the blood-sugar is already low. It is desirable before adopting insulin treatment to try the effect of dieting, and when the patient is doing fairly well on diet insulin should not be given. If however the blood-sugar still remains high, the additional carbohydrate requires to be metabolised by the administration of insulin. Since 1 unit will ensure metabolism of 2 grm. of sugar, the daily dose should be in proportion of half of the daily amount excreted in grammes, and should be given in 2 to 3 divided doses half an hour before meals followed by some sugar.

Result of overdosage — A dose of insulin which will lower blood-sugar in rabbits to 0.015 p.c. or less causes increased reflexes, rapid and shallow respiration, clonic convulsion, coma and death. These symptoms are arrested by the administration of glucose. In man the symptoms of hypoglycaemia are observed when insulin is given in very large doses, or when the supplement to the diet is not given in the proper time relation. The severity of the symptoms depends upon the fall of blood-sugar. When the blood-sugar content is 0.07 p.c. the patient only experiences a sense of uneasiness and nervousness with a feeling of impending danger. When it is below 0.06 p.c. there is weakness, nervousness, dizziness, disturbances of sight and profuse perspiration. If the sugar is reduced still further, *i.e.* 0.04-0.055 p.c., there is aphasia, disorientation, mental confusion, loss of reflexes, and perhaps coma and death. The symptoms are possibly due to defective supply of glucose to the nerve cells of the brain, and are rapidly removed by the administration of some carbohydrate. Insulin exerts its maximum effects about four to five hours after injection, therefore the symptoms of overdosage appears at this time. These symptoms are induced or aggravated by exercise; and all patients should be warned of this possibility and should be advised to keep some sugar preparation for an emergency. An ounce of glucose or other sugar solution may be given by the mouth. If the patient is unconscious or the symptoms have lasted long, it is necessary that glucose should be given by intravenous injection, 5 to 20 grms. being given in 50 to 100 c.c.

water. Adrenaline is often useful but is not so certain as glucose as its effect depends upon the availability of glycogen in the liver, which may be present in very small amount, so that even if adrenaline is given glucose should also be administered.

Conclusion.—Insulin is not a cure for diabetes, but it is a valuable aid to the physician specially in cases of diabetic coma. It has helped diabetic patients to undergo surgical operations without any danger. The only drawback is that its effects do not last long, and it has to be used for an indefinite period, at least in some severe cases, while in others it fails to make the urine sugar-free.

The importance of distinguishing diabetic coma from insulin coma is obvious, and Graham gives the following points for distinguishing them:—*

Insulin Coma	Diabetic Coma
1. Skin usually very white, may be normal in colour.	Skin usually flushed.
2. No smell of acetone in breath.	Breath smells of acetone.
3. Respiration shallow.	Respiration deep (abdominal respiration is characteristic).
4. Urine usually sugar-free, except when bladder was not emptied for some hours or blood-sugar was above 200 mg per 100 c.c.	Always contains large amount of sugar.
5. Eyeball tension normal or raised.	Eyeball tension much lower.
6. Urine need not contain aceto-acetic acid.	Urine always contains large amounts of aceto-acetic acid.
7. Blood-sugar below 70 mg. per 100 c.c., may be below 40 mg.	Blood-sugar over 200 mg. per 100 c.c. may be even 500-800 mg.

PROTAMINE INSULIN *Syn—Insulin Retard.*—A compound of insulin hydrochloride with a protamine obtained from the sperm of a species of trout. It is injected as a colloidal suspension formed by the addition of sodium phosphate which precipitates protamine insulin with a pH of 7.3. This compound prolongs the action of insulin.

PROTAMINE-ZINC-INSULIN.—The addition of zinc to protamine insulin helps still further to prolong the duration of blood-sugar lowering effect as also its stability. It contains 40 units per c.c.

ACTION AND USES

Protamine-zinc-insulin is more slowly absorbed than unmodified insulin. Therefore it is used in those cases where the original insulin requires to be administered in several doses daily, or it causes frequent hypoglycaemic reactions. Whereas maximum reduction of blood sugar with unmodified insulin takes place in about 2 to 3 hours, the greatest effect of protamine-zinc-insulin does not develop till after 6 to 10 hours, and the effect lasts for 24 to 30 hours. The fall of blood sugar is therefore gradual and the rapid alteration of blood sugar level which follows the administration of original insulin is obviated. Since its absorption is slow

* G. Graham. *Medical Press and Circular*, 1934, Symposium No. 1

and the effects do not show themselves till several hours after administration, it cannot control a carbohydrate meal taken soon after the injection. It is therefore necessary sometimes to give an injection of ordinary insulin before breakfast to deal with the blood sugar rise from this meal and then administer protamine-zinc-insulin to maintain the sugar within normal level during the rest of the day.

Protamine-zinc-insulin may be administered once a day either in the morning one and one-half hours before breakfast, or one hour before the last meal or an hour before retiring, or half the required dose may be given in the morning and the other half in the evening.

When treating patients with protamine-zinc-insulin, owing to the slow action, the full effect of the treatment will not be observed until a week or two after the initial administration. Therefore one should not increase the dose if no benefit is observed during the first few days of its administration.

Protamine-zinc-insulin hypoglycemia.—Hypoglycæmic reactions after this remedy is not so frequent as after the use of unmodified insulin. Owing to its slow action these come on very slowly and are often missed, owing to the symptoms being less definite. Vague symptoms of fatigue, headache, drowsiness, lassitude, tremulousness, and nausea should be looked upon with suspicion. The typical symptoms of hypoglycemia following ordinary insulin may however appear suddenly with some patients. The appearance of any of these symptoms calls for immediate treatment and since the supply of insulin to the tissues is slow and continuous the treatment must be prolonged.

GUANIDINE

(*Not official*)

Guanidine or *Imido-urea* is found in certain plants and can also be obtained from certain proteins. It resembles physostigmine in action, and at one time was considered responsible for the causation of idiopathic tetany of children and related to parathyroid metabolism. It has however the property of reducing blood-sugar and producing hypoglycemia. Subsequently Frank and others introduced Synthalin and Synthalin-B, both guanidine derivatives, with properties similar to those of insulin, but without its toxic effects and which unlike insulin are effective when administered by the mouth. How synthalin acts is not known, but it is possible that it acts either by lowering the cellular threshold for glucose-insulin metabolism, or more probably, by depressing glycogenolysis, thereby increasing the secretion of endogenous insulin. It is extolled by some but so far the results have not been uniform.

Some patients show intolerance to synthalin. The symptoms are vague dyspepsia, feeling of weight in the upper abdomen, flatulence and feeling of distension, constipation or often looseness with colicky pain, loss of weight and general malaise and languor. These symptoms are rare when a high carbohydrate and a low fat diet is given.*

* Todd, Brinckman and Sansom, *The Practitioner*, May 1932

Synthalin—Decamethylene diguanidine bihydrochloride. *Dose*— $\frac{1}{16}$ gr. or 0.01 gm.

Synthalin-B—Dodecamethylene diguanidine dihydrochloride. *Dose*— $\frac{1}{12}$ gr. or 0.005 gm.

XT ACTU SUP A NALI CORTICIS, B.P.C.

Extract of Suprarenal Cortex. (Not official)

Syn.—Cortin.

An extract containing the specific principle of suprarenal cortex which, when injected, prolongs the life of cats or dogs from which the glands have been removed.

Dose— $\frac{1}{4}$ to $2\frac{1}{2}$ drs. or 5 to 10 mils

ACTION AND USES

In 1856 Brown-Sequard following the classical description of the clinical picture of chronic adrenal insufficiency (Addison's disease) attempted to reproduce the Addisonian syndrome in animals. The rapidly fatal results (the animals only survived for a few hours) led him to conclude that the adrenals were indispensable to life.

While many aspects of cortical function are still obscure, experiments during the past decade have thrown much light on this vital and hitherto little understood endocrine gland. The chief functions of the cortex may be summarised as follows: (a) It maintains normal blood volume by control of excretion and resorption (in the kidney tubules) of electrolytes and water; (b) it acts as a general tissue and cell catalyst, specially with regard to the hepatic function; and (c) it plays an important part in carbohydrate metabolism, specially in respect to glycconeogenesis. There is evidence to indicate that it is closely related to urea formation, to vitamin C storage, to cholesterol metabolism, and to resistance to infection and toxæmia. Some believe that it is a factor in the normal healing of wounds and callus formation. It is possible that it causes leucocytosis and strengthens their phagocytic activity.

Its removal is followed, after a few days, by extreme depression, increasing muscular weakness, passing into complete prostration terminating in death. It is therefore essential for the sustenance of life; but all attempts to explain why it should be so have not been successful. Loeb (1935) pointed out that it was related to metabolism of sodium chloride and that its removal was followed by increased elimination of sodium in the urine and corresponding diminution of serum sodium, *i.e.* bicarbonate and chloride of sodium was diminished. The fluid became depleted and the body suffered from dehydration. In man its destruction or disease is followed by pigmentation of the skin, low blood-pressure, muscular weakness, vomiting and death—symptoms of Addison's disease. The basal metabolic rate is diminished to the extent of 25 p.c. The cortex is also intimately related to the sexual organs, and its over-activity inhibits the development of female sex glands. Women suffering from tumours of the cortex show signs of virilism, hirsutism and atrophy of the breast and uterus.

It is largely used in the treatment of Addison's disease which is associated with degenerative changes in the cortex, and it supplies the hormone absent in this disease. Its administration is followed by the disappearance of nearly all the signs and symptoms of the condition. The usual method of treatment is to give it subcutaneously, intramuscularly or by intravenous route 10 to 20 c.c. in divided doses daily with injections of sodium chloride which enhances the action of this hormone.

Its use has also been suggested in cyclical vomiting, infantile diarrhoea of uncertain origin, vomiting of pregnancy, and severe infec-

tions.* But it appears that unless more is known of this gland its use must perforce be empiric in these conditions.

Action of other Hormones

The exact manner in which the different animal extracts or their active chemical substances produce their characteristic effects is still a matter of speculation. But it is generally believed that some act by influencing the cell metabolism, while others through the sympathetic or parasympathetic systems. There can be no doubt that thyroid affects metabolism by acting on the different cells of the body, while the action of pituitary is specific and affects only certain types of cells. Adrenaline on the other hand produces its effects through the medium of the autonomic nervous system.

These different organs by virtue of their internal secretion, either severally or jointly, exert a controlling influence on the general metabolism of the body. In some cases they augment, while in others neutralise each other's action. Therefore total or partial removal of any of these organs is followed by a complex series of effects. Thus the metabolism of carbohydrate is controlled by thyroid, suprarenal medulla, pituitary and pancreas; and while the suprarenal, pituitary and thyroid produce glycogenolysis and glycosuria, pancreas antagonises this effect. Similarly the development of secondary sex characters is also influenced by several of these glands, of which the gonads are the most important, although adrenal cortex and anterior pituitary are also intimately associated.

The different endocrine organs are used therapeutically for the following objects:—

1. *Substitution Therapy.* This it does by supplying the missing hormone the loss of which is known, *e.g.* the use of thyroid in cretinism and insulin in diabetes mellitus.

2. *Supplemental Therapy*—This is done by supplying a presumed deficiency, due either to an increased demand or decreased output. It is possible that in some instances the improvement is due to stimulation of the analogous organs to increased activity, when it is known as *homostimulation*.

3. *Physiological Therapy.* In this advantage is taken of our knowledge of pharmacology of certain gland extracts, and they are used to produce definite effects either through the sympathetic nervous system, or directly on the tissues concerned, and not through any alteration in the normal hormone product, *e.g.* adrenaline and pituitary extract.

THE THYROID GLAND

There are two classes of disease associated with abnormality of the thyroid gland:

1. Those in which there is an absence of the internal secretion.
2. Those in which the internal secretion is either abnormal or excessive.
 1. The treatment by means of thyroid extract has been fully dealt with (*see page 606*).
 2. Under this head is exophthalmic goitre or Graves' disease. Numerous methods have been devised with the object of neutralising excessive and abnormal secretion to which the unpleasant symptoms of the disease are believed to be due.

The chief of these are the following:—

1. The use of the milk of thyroidectomised goats.
2. „ the serum of thyroidectomised sheep.
3. „ thyrolytic serum.

*Kemp, *British Medical Journal*, June, 12, 1937

1. The Milk of Thyroidectomised Goat

The theory of this remedy is that when the goat has been deprived of its thyroid its milk will contain an excess of the toxin which is normally destroyed by the thyroid, and hence will tend to neutralise excessive thyroid activity. This method of treatment has obvious disadvantages and it has been given up in favour of the next method, which depends upon similar principles and is easier to carry out.

2. The Serum of Thyroidectomised Sheep

This is obtainable in two forms:—

- 1 Moebius's Serum or Antithyroidin.
- 2 Thyroidectin.

(1) *Moebius's Serum*.—This is blood serum obtained from rams six weeks after extirpation of the thyroid, to which 0.5 p.c. phenol has been added as a preservative. It is said to keep indefinitely and is therefore more generally useful than the milk, besides which it probably contains a larger proportion of toxins. The patient becomes quiet, sleeps better and puts on weight, whilst both the exophthalmos and the swelling subside. The amount of serum to be used varies in different cases and the amount given cannot be increased indefinitely; otherwise there is danger of producing symptoms of athyroidism, namely a mild type of myxœdema with headache, apathy and mental stupidity.

Administration.—Until recently it was given by the mouth, either in solution or in tablets. But the intramuscular injection appears to be the best.

Dose.—*Intramuscular*, ordinarily about twenty injections of 1 c.c. each is required, but in severe cases as many as thirty, once a day for the first fortnight and later one every two or three days only.

By mouth, the serum 10 drops three times a day, increasing every day by 5 drops till 30 drops are given per dose, and then to reduce it the same way. After 50 c.c. in all have been given, the treatment should be stopped for a week, and can be resumed again for a short period with 10 to 20 drops three times a day.

(2) *Thyroidectin*.—This is a brown powder prepared by inspissating the serum of thyroidectomised animals. Its use is similar to that to Moebius's serum. **Dose**.—5 grs. in capsule.

3. Thyrolytic Serum

Beebe has prepared an antithyroid serum, which not only contains a specific cytotoxin, but also has the power of neutralising the thyroid secretion. He accomplished this by isolating the nucleo-proteins and the thyroglobulin of two glands removed from patients with exophthalmic goitre and injecting these into rabbits. This serum, being made from human organs is capable of doing great harm to man and must therefore be used very cautiously and in small doses slowly, not more than 1 c.c. for injection.

THE THYMUS

Persistent enlargement of the gland in exophthalmic goitre led to the belief that this enlargement was conservative, and preparations of thymus gland were used in the treatment of this disease with very doubtful results. On the other hand some hold that its persistence is the cause of Graves' disease. It has also been used in a variety of conditions including nutritional disorders in children, but there is little positive evidence of its value. Given in tablets, 2 to 4 grs.

MUSCLE EXTRACT

Within recent years extract of mammalian tissue has been used in the treatment of cardiac and circulatory disturbances. A preparation called *Lacarnol* (extract of heart muscle) has been placed on the market and is claimed that it has a specific action in dilating the vessels, specially coronary arteries. The indications for its adminis-

tration are cardiac failure, arrhythmia, angina pectoris, intermittent claudication, and (occasionally) hypertension. There is evidence that muscular exertion liberates antispasmodic and vaso-dilator substances, which sometimes prevent anginal attacks or intermittent claudication. Muscle extract is specially useful in spasmodic angina; attacks due to cardiac dilatation or coronary thrombosis are seldom if ever relieved. Apart from these vaso-dilator and antispasmodic effects, muscle extracts appear to have a cardiotonic and regulating action, relieving decompensation and arrhythmia. The action sometimes resembles digitalis, in fact the effect is very definite when both are given in combination. It is still in its experimental stage.

It may be used both *hypodermically* and by *mouth*. The dose of Lacarnol is 10 to 25 drops, once or thrice daily, or 1 c.c. hypodermically. Another preparation is **Sarcolan**, dose 1 c.c. hypodermically.

THE BONE MARROW

This is the bone marrow obtained from ribs and flat bones. Red bone marrow contains largely (about 90 p.c.) of fat and in new born animals one-third of the fat is lecithin; it also contains iron in organic combination.

It is supposed to stimulate the formation of red blood corpuscles. This action is probably due to the presence of iron and lecithin. It is used as a remedy in **pernicious anæmia**, **chlorosis**, **scurvy**, **purpura**, **hæmophilia**, **debility**, **leucocythæmia**, **lymphadenoma**. Owing to the presence of active cholesterol, fresh red bone marrow has a distinct **antirachitic** value.

It can be administered in the fresh state, but it is difficult to prepare, and is better as a rule to use one of the various preparations that are on the market, *viz.* 1. **Bone Marrow Tabloids**. -3 grs. each; **Virol**; and **Marrubin**, a glycerin extract of ox-bone marrow, as a palatable substitute for cod-liver oil. *Dose.* 1 to 2 drs.

THE SPLEEN

Hormonal (extract of spleen) injected subcutaneously increases intestinal peristalsis and acts as a purgative (page 343). Its effects are however uncertain, and sometimes produces dangerous symptoms and even fatal effects. It was believed that the purgative effect was due to the presence of a special hormone, but since other organ extracts produce similar effects, it is possibly due to the presence of histamine, choline or other products of tissue katabolism. Usual dose is 15 to 20 c.c. Two forms are issued, one for intramuscular injection, the other for intravenous injection. Castor oil one ounce should be given simultaneously.

An extract of pig's spleen has been used with success in the treatment of **tuberculosis**. The usual dose is 5 c.c. for adults *intramuscularly* into the thigh, or *subcutaneously*, twice a day. It has been credited to stimulate calcium metabolism and to possess hæmostatic properties, and has been used in menorrhagia and anæmia.

GROUP XXIII

DRUGS ACTING ON THE BLOOD

Changes in the blood both in quality and quantity may occur necessitating the use of remedial measures. The most important change occurs with regard to the red blood cells. They may be diminished in number, or there may be deficiency of hæmoglobin, and since the oxygen-carrying power of the blood depends upon the amount of hæmoglobin in the corpuscle, deficiency of hæmoglobin, *i.e.* anæmia, demands early

treatment. Iron is its chief constituent and the body contains about 3 grm, and about two-third of the iron in the body exists in the form of hæmoglobin, the rest is stored in the liver, spleen and other tissues by the reticulo-endothelial cells.

Normally the red blood corpuscles have an average life of about three weeks, hence they require constant renewal to maintain the red blood cells at the normal level. These are manufactured in the red bone marrow. Drugs which increase the number of red blood corpuscles are known as hæmatinics.

Diminution of the red blood supply to the blood-forming organs acts as a stimulus and causes regeneration of the red blood cells. On the basis of this theory venesection has been done in chlorosis to stimulate the inactive bone marrow.

Hæmatinics have no effect in increasing the amount of iron in healthy blood. They act only when either the hæmoglobin or the number of red corpuscles are deficient. The red blood corpuscles are manufactured in the red bone marrow. Arsenic causes hyperæmia of red bone marrow, and liver extract causes increased formation of red blood cells. Iron and its salts, and desiccated stomach are also valuable hæmatinics.

In order that the student may understand the rational treatment of anæmia it is necessary that he should have a clear conception of the underlying factors which produce the condition.

Recent studies have brought to light the different factors which control the formation of the red blood cells in the bone marrow. A special hæmatinic (anti-anæmic) principle, is necessary for the development of the megaloblast to the erythroblast stage, and the relationship of iron in the transformation of the erythroblast into a mature erythrocyte has long been recognised. Small quantity of copper is necessary for the synthesis of hæmoglobin, while thyroxine and vitamins B and C are also of value in helping formation of red cells.

Anæmia has been classified broadly into the following two groups:—

A Macrocytic Hyperchromic Anæmia.—Pernicious anæmia is the typical example of this variety, and is characterised by a reduction in the number of red cells, which become abnormal in shape and size (tend to become larger), but the hæmoglobin is correspondingly less diminished so that there is a high colour index (hyperchromic). The blood maturing function of the red bone marrow is disturbed from the absence of the antianæmic principle which is stored in the liver. This principle is formed in the stomach by the interaction of an enzyme present in the gastric juice (*intrinsic factor* or *hæmatinic principle* of Castle), with another substance pre-

sent in meat, yeast and other foods and possibly vitamin B complex (*extrinsic factor*). This specific antianemic factor is stored in the liver and after interaction with bone marrow forms normal blood. This liver principle has been isolated in a relatively pure form by Dakin and West* under the name of "anahæmin." It follows therefore that any breakdown in the above chain will cause macrocytic anemia as a result of the failure of megaloblastic maturation.

(a) The breakdown may be in the intrinsic factor due to failure of the stomach to secrete the special enzyme. Possibly responsible for Addisonian pernicious anemia.

(b) The breakdown may be in the extrinsic factor. Malnutrition (absence of high grade proteins and fresh vegetables) specially in the tropics is an important factor in the production of megalocytic hyperchromic anemia. The anemia of pregnancy is believed to be due to the absence of this factor and is successfully treated with proper diet and autolysed yeast.

(c) Both factors may be present, but owing to the abnormal state of the intestinal canal it may fail to absorb and utilise the hæmatinic principle. This possibly occurs in the presence of intestinal parasites or when there is impermeability of the intestinal mucosa. Faulty absorption of the hæmatinic principle is perhaps the cause of the failure to respond to liver administered by the mouth, though these cases improve when administered by intramuscular injection.

According to Castle† all the above factors are at work in tropical sprue.

(d) Faulty storage of the hæmatinic principle (P.A. Factor). It is possible that associated with this fault there is also mineral deficiency, and these cases improve when iron is given with liver. In cases of megalocytic hyperchromic anemia associated with intestinal lesion this dual deficiency may be present.

B. *Microcytic Hypochromic Anæmia*.—This is primarily due to iron deficiency either in the diet, *e.g.* nutritional anemia of infants; or when absorption of iron is defective consequent on achlorhydria (chlorosis falls under this group), or when there is increased demand for iron, as in pregnancy, menorrhagia, etc.

A mild form of anemia of this variety may occur in thyroid deficiency, which is cured by a course of thyroid. Iron and copper, also vitamin C are necessary for the transformation of erythroblasts to erythrocytes.

Anæmia after hæmorrhage is also of microcytic type which responds to iron therapy, so also anemia due to some toxins (toxic anemia), *e.g.* anemia of malaria, and other infectious diseases.

**Jour. Biol. Chem.* 1935.

†*Lancet*, 1932, Vol. 1.

The anæmia of pregnancy may be of the microcytic type from deficiency of iron in the diet, or from defect in the absorption of iron from disturbances in the stomach and intestine, or from excessive drainage of iron. These improve under iron. But the intrinsic factor may also be involved leading to the pernicious type of anæmia.

Aplastic anæmia is a condition where the activity of the bone marrow is entirely suspended, and generally follows the use of certain drugs, *viz.* lead, mercury, benzene, etc. Arsenic causes some hyperæmia of the red bone marrow and is often used, although its exact mode of action is not known. Repeated transfusion of blood has been recommended in the hope that the bone marrow may regain its hæmopoietic functions.

White blood corpuscles.—These corpuscles are migratory in their habits, and in case of inflammation they wander through the capillary walls. Salicylic acid, quinine and other cinchona alkaloids arrest their movements in very dilute solutions, while in concentrated solutions they are destroyed. They are also destroyed by X-rays and benzol.

Counter-irritants at first cause leucopenia followed by leucocytosis. Salts of calcium increase their activity and the phagocytic power in a definite manner. White blood corpuscles are increased by (a) pilocarpine, which causes contraction of smooth muscles of the spleen and lymphatic glands; (b) bitters and volatile oils, which irritate the mucous membrane of the intestine; (c) radium, which causes irritation of the blood-forming organs; and (d) injection of a foreign protein like milk.

Coagulation of blood.—One of the most important functions of the blood is its power to coagulate shortly after it leaves the blood vessels. The essential part of the clot is fibrin, an insoluble protein compound not normally present in the circulating blood, but formed from fibrinogen present in the plasma by the action of thrombin. In the circulating blood thrombin exists as inactive prothrombin which is changed to thrombin by the addition of tissue extracts, which contain lipid thromboplastic substances (thromboplastin, thrombokinas, cephaline); possibly by a similar substance liberated from the disintegration of blood platelets after hæmorrhage; and by the presence of minute amounts of ionised calcium salts.

Drugs increasing the coagulability of the blood.—Coagulation of blood can be increased therapeutically by the administration of calcium salts; transfusion of whole blood not only to replace the lost blood but also to supply any elements that may be lacking; normal serum, which contains some thrombin and thromboplastin; and cephaline, a lipid obtained from ox brain; by congo red and snake venom.

Congo Red.—A reddish brown powder, soluble in water. Used in-

travenously in the treatment of internal hemorrhages, specially hæmoptysis, and as a diagnostic agent in amyloid disease. It increases the number of monocytes, fibrin and blood platelets and induces thrombocytosis, and causes a reduction of clotting time.

Dose. -5 to 10 c.c. of 1 p.c. solution, *intravenously*, repeated after 4 to 6 hours.

Snake Venom. -The venom which increases coagulability of the blood and therefore stops bleeding is that of Russell Viper Venom, which may be applied whenever the bleeding point is accessible. **Moccasin Venom** given subcutaneously or intradermally decreases the permeability of capillaries and stops remote hæmorrhage, but not in hæmophilia. **Dose.** -0.4 mil of 1 in 3000 solution.

Drugs decreasing the coagulability of the blood.—Coagulating power of the blood is diminished by inactivating the calcium by citrates or oxalates. Leech extract or hirudin contains an anticoagulant substance which prevents clotting. Similarly heparin obtained from liver increases the anti-thrombin of the blood.

Hirudin.—It is largely used in laboratory experiments. gr. 1 will keep 1000 c.c. of blood in a fluid condition for a considerable time. It has been used as an anticoagulant in blood transfusion. The dose being 0.02 to 0.3 gm. in 50 mil of normal saline.

Heparin. A purified liver extractive possessing anticoagulating property by increasing antithrombin in the blood. It is injected intravenously for the prevention of thrombosis in blood transfusion. In concentration of 1 mg. in 100 c.c. of blood it prevents clotting for 24 hours. **Dose.** 1 mg. in 10 c.c. of saline for each 100 c.c. of blood to be transfused.

The plasma.—The chief function of the plasma is to carry nutrient materials, hormones and drugs to the different tissues, and the excretory products to the kidneys. The plasma proteins help conversion of fibrinogen into fibrin when blood is shed. By exerting an osmotic pressure they tend to retain fluid in the capillaries and help to maintain the blood volume, regulate interchange between the blood and the tissue spaces and influence the filtration in the glomeruli in the kidney. The plasma contains and can develop immune bodies, *e.g.* agglutinins, precipitins, opsonins, etc., and obviously is of great value both in health and disease.

Reaction of the blood.—The normal reaction of the blood is almost neutral or weakly alkaline with a pH of 7.3 to 7.5, and life is incompatible when the pH of blood is below 7.0 or above 7.8. The maintenance of the pH at its normal level in the blood and tissues is regulated by the carbonates and alkaline phosphates which form the alkaline reserve, and by the carbonic acid, the phosphates and proteins which form the acid reserve. The body is protected from the harmful effects due to variations of reaction not only by the buffer action of these salts, but also by the lungs, kidneys, and probably the intestine. The lungs get rid of the excess of CO₂ and the volatile acids (oxybutyric acid series) and the kidneys by increased excretion of fixed acids, and by increased ammonia formation.

Acidosis.—By acidosis is meant a condition in which the reaction of the blood is less alkaline than normal, and the blood is taken as an index of the reaction of the tissues generally. This may happen when the alkaline reserve of the body is depleted. Acids are always being produced in the body as a result of katabolic activity, but provision is made for their neutralisation and excretion through the buffer action of the blood and tissues, and the excretory functions of the lungs and the kidneys. So long as this production of acid remains within normal limits and the organs concerned in its removal are functioning, there is no evidence of their disturbance. Of the acids, phosphoric, sulphuric and lactic and the other organic acids are neutralised as soon as they are formed, so that they are always present in the blood and tissue fluids as salts. CO_2 on the other hand is not completely neutralised and is found in the blood as a free acid in solution. In herbivorous animals owing to their food being rich in potassium and sodium, the acids are eliminated as salts of fixed alkalies, and the blood becomes depleted of its store of fixed alkalies when a large amount is lost. In carnivorous animals and in man there is no such loss as the acids are excreted in combination with ammonia, because their food contains little fixed alkalies and the acid products of metabolism are neutralised by ammonia liberated by the tissues thus protecting the fixed alkalies. In acid poisoning therefore ammonia salts excreted by the urine are increased. This protection is normally present but may fail when there is increased production of acids, as in diabetes due to defective oxidation of the products of fat metabolism resulting in the accumulation in the body of substances known as ketone bodies, *viz.* acetone, aceto-acetic acid and β -hydroxybutyric acid (ketosis); in nephritis from diminished excretion of acid; after exercise, and in arsenic and phosphorus poisoning from excessive production of lactic acid; by the use of large doses of ammonium and calcium chloride; or by adding to the body one of its acid elements, *viz.* chlorine. Interference with the excretion of CO_2 by the lungs so that it may combine with water to form carbonic acid (H_2CO_3) which dissociates to yield H^+ -ion, also increases the hydrogen-ion concentration of the blood. Minor degree of acidosis is also present after fasting specially with a low carbohydrate diet, in chloroform narcosis, etc. The term ketonæmia or acetonæmia signifies the presence of ketone bodies in the blood above 3.0 mg. per cent., and ketonuria or acetonuria their presence in the urine.

Alkalosis.—By this is meant a condition in which the blood is more alkaline than normal. Owing to the ease with which the body can accumulate acids, alkalosis is not so common as acidosis, but a mechanism exists to prevent the

reaction of the blood and tissues from becoming too alkaline. It occurs clinically in persistent vomiting, and in high intestinal obstruction and pyloric obstruction, due to loss of hydrochloric acid, so that there is uncompensated acid deficit and accumulation of bicarbonates; by forced breathing, thereby eliminating an excess of CO_2 from the alveolar air thus lowering the CO_2 tension in the arterial blood; by calcium deficiency, as after parathyroidectomy or tetany; and by the use of large doses of alkalis as may happen in the treatment of peptic ulcer, provided the kidney function is impaired. Symptoms of alkalosis are: nausea, distaste for food, headache, weakness. Severe forms are followed by tetany, oedema and delirium.

Toxicology of blood.—Certain drugs like arsenious acid, phosphorus, iodine, sulphur, oil of turpentine and hydrocyanic acid reduce haemoglobin in poisonous doses. Alcohol and quinine bind oxygen so firmly to haemoglobin that its oxygenating power is impaired. Phenazone, phenacetin and acetanilide, potassium chlorate, nitrites and sulphanilamide convert a portion of haemoglobin into methaemoglobin in poisonous doses. In sulphonal poisoning haematoporphyrin is formed which is excreted in the urine.

Haemolysis or destruction of red blood cells also occurs when the osmotic pressure of the surrounding fluid becomes lower than the corpuscles, as happens when the blood is greatly diluted with pure water. Conversely haemolysis may occur if the blood corpuscles have a higher osmotic tension than normal plasma, as happens when concentrated salt solution or pure glycerin is injected into the tissue. Besides the osmotic changes, saponins, ether, chloroform in sufficient concentration act as haemolytics. In practical therapeutics this is unimportant as saponins do not enter the blood unchanged from the intestine, and the narcotics do not reach the blood in sufficient concentration to produce any haemolytic effect.

Class A : Drugs used in Macrocytic Hyperchromic Anæmia

EXTRACTUM HEPATIS SICCI

(Ext. Hepat. Sicc.)

Dry Extract of Liver

Syn.—Extract of Liver.

Source. It is a selected fraction of an alcoholic extract of ox or sheep liver, and contains the specific principle, which increases the number of red corpuscles in the blood of persons suffering from pernicious anaemia.

Characters.—A light, brown, very hygroscopic powder; odour, faintly meatlike; taste, saltish and meatlike. *Soluble* in water, almost insoluble in alcohol (90 p.c.).

B.P. Dose. The quantity equivalent to 225 grm. or about half a pound of fresh liver.

OFFICIAL PREPARATION

1. *Extractum Hepatis Liquidum*—A selected fraction of an alcoholic extract of ox or sheep liver, dissolved in a mixture of glycerin, alcohol and distilled water. Contains the specific principle which increases the number of red blood corpuscles in pernicious anæmia 1 oz. is equivalent of 8 oz. of fresh liver B.P. Dose.—1 oz. or 30 mils.

NON-OFFICIAL PREPARATION

1. *Liquor Hepatis Purificatus*, U.S.P.—Purified solution of liver; contains soluble fraction of mammalian liver which increases the number of red blood corpuscles Used for injection. Dose—Stated on the label.

PHARMACOLOGY AND THERAPEUTICS

Liver furnishes a material which acts as a specific in the treatment of different types of hyperchromic macrocytic anæmia, e.g. pernicious anæmia. It supplies a substance which acting on the bone marrow brings about maturation of the red cells and which substance is missing or not available in this disease. In pernicious anæmia the hydrochloric acid becomes deficient and there is gastro-intestinal stasis, and it is possible that constant absorption of toxins prevents the formation of this substance. The anti-anæmic factor is produced in the stomach (see p. 326) from the interaction of a gastric ferment (intrinsic factor of Castle or hæmopoietin of Wilkinson), and an extrinsic factor formed by the protein as the result of gastric digestion. The antianæmic principle is essential for the proper maturation of the megaloblasts in the bone marrow into normoblasts and reticulocytes. The nature of the extrinsic factor is still unknown although some workers suggested that it was closely allied, if not identical, with vitamin B₁₂, but this has not received confirmation. Evidence is accumulating which suggests that the effective hæmopoietic principle in liver is probably a combination of factors with somewhat different action, and it is possible to isolate three chemical substances from liver which exert varying effects on hæmopoiesis in animals and man and which to obtain maximum effect in man should be given together.*

The value of liver treatment is well established in (a) *tropical megalocytic hyperchromic anæmia*; (b) *Addisonian pernicious anæmia*; (c) *tropical sprue*; (d) *pernicious anæmia of pregnancy*; and (e) *megalocytic hyperchromic anæmia* associated with infestation of the intestine with some parasites, lesions of the gastro-intestinal tract, and disease of the liver. All these anæmias have certain morphological features in common, they are megalocytic and hyperchromic, and the bone marrow shows hyperplasia of the more primitive red cells. Minot and Murphy claim that patients having a count of red blood cells below 2,700,000 showed marked

**Jour. Amer. Chem. Soc.* 1936.

marked improvement after a diet of liver within one month. The blood picture of a patient showing 1,509,000 red blood cells before treatment went up to 3,360,000 after one month, 4,250,000 and 4,650,000 after two months and four to six months respectively. Along with this improvement the general condition improves, the appetite returns, and weakness and depression disappear rapidly.

Liver has also been used to counteract certain unpleasant toxic effects which follow the administration of arsenic and bismuth, and it has been used in the dermatitis which follows the use of these drugs.

Prolonged administration of liver has been advocated in hæmophilia on the theory that it plays an important part in the production of those factors essential for coagulation of blood.

Owing to the presence of a depressor principle, hepatic extract is said to lower blood-pressure by facilitating detoxication, and has been recommended in the treatment of arterio-sclerosis. The blood-pressure may fall temporarily owing to the presence of choline and histamine in the extract but not to any specific liver secretion. It has however repeatedly failed in the writer's hands when given in carefully selected cases both by the mouth and subcutaneously.

Liver is rich in vitamins, specially vitamin B complex.

Mode of administration.—For therapeutic purposes the liver of sheep, goat, oxen and calf are used, and may be given either in the dry form or as liquid extract, or cooked according to the taste and choice of the patient, but prolonged cooking should be avoided. Half a pound daily of cooked liver is sufficient to bring about a prompt response. One ounce of the liquid extract is equivalent to half a pound of the fresh liver. But there are obvious disadvantages of using daily large amounts of liver which the patient very soon begins to dislike or may be unable to tolerate owing to gastro-intestinal disturbance. To obviate these difficulties liver extract may be used. Ordinarily administration by the mouth is sufficient, but in cases of severe relapse or when rapid action is necessary, the intramuscular or the intravenous route may be adopted. Experience has shown that parenteral administration intramuscularly is more efficacious and economical than oral use. Although the greatest benefit is derived from intravenous method of administration, the general use by this route has potential dangers, and the routine method should be by the mouth, or by intramuscular injection. The dose for intravenous use is 0.1 gm. per kilo of body weight dissolved in physiological salt solution, so that 20 c.c. should contain 1 gm. of liver. It is necessary that the active principle should be sufficiently purified to avoid any allergic phenomena or a fall of blood-pressure. Preparations for intramuscular or intravenous use are many

and these are given once, twice or oftener a week as may be necessary, *e.g.* Anahæmin, 1 to 2 c.c.; Hepatex-T, or Cam-polon.

Untoward effects.—Injection of liver extract is sometimes followed by certain reactions. They are classified as follows: pain and local reaction; acute fall of blood-pressure; and allergic manifestations such as urticaria, collapse, dyspnœa, and generalised erythema.

VENTRICULUS ESICCATUS, B.P.C.

Desiccated Stomach. (Not official)

Syn.—Ventriculin; Gaster Sicca

Source.—Whole desiccated stomach of hog, sheep or oxen, defatted with petroleum benzene. No taste, and very little odour

Dose.— $\frac{1}{4}$ to 1 oz. or 8 to 30 grm.

ACTION AND USES

Castle and Townsend have shown that healthy stomach secretes a substance which when absorbed acts upon the bone marrow in such a way as to bring about maturation of the red blood cells. This is supposed to be stored either in the liver, kidneys or other organs. This antianæmic factor is produced in its greatest concentration in the pyloric portion of the stomach and the duodenum and is formed by the action of an intrinsic factor which is probably an enzyme, present in normal gastric juice upon an extrinsic factor present in meat, yeast, etc. It is assumed that patients suffering from pernicious anæmia do not secrete this antianæmic substance, and the failure of the red bone marrow cells to mature in this disease is associated with the inability of the patient to develop the blood-maturing substance. Subsequently Isaac and Sturgis have shown that desiccated and defatted chopped up gastric tissue contains in abundance this active substance. Desiccated stomach therefore has been used in the treatment of macrocytic hyperchromic anæmias, *i.e.* pernicious anæmia, hæmolytic anæmias associated with pregnancy and sprue, and other macrocytic anæmias, and cases intolerant to liver. The usual dose is 15 grm. of the dried material corresponding to 100 grms. of the fresh stomach. Safe clinical dose is 10 grm. for each million red cell deficit in the count. When the blood returns to normal it should be continued in 10 grm doses four to five times a week. The best form of administration is in some fruit juice or milk but not in hot fluids.

Class B: Drugs used in Microcytic Hypochromic Anæmia

FE U

Iron. (Ferr.)

Syn. I V.—*Loha*, Beng., Hind.

Source.—Iron in the form of fine bright wire having a diameter of about 0.1 millimetre.

OFFICIAL PREPARATIONS

1. **Syrupus Ferri Iodidi.**—Contains $7\frac{1}{2}$ grs. of ferrous iodide, or $1\frac{1}{2}$ gr. of iron in 120 ms. B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

2. **Syrupus Ferri Phosphatis Compositus.** *Syn.*—*Parrish's Food*, *Parrish's Syrup*; *Chemical Food*.— $1\frac{1}{2}$ gr. ferrous phosphate, or $\frac{1}{2}$ gr. iron, $1\frac{1}{2}$ gr. tricalcium phosphate in 120 ms. B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

3. **Syrupus Ferri Phosphatis cum Quinina et Strychnina.** *Syn.*—*Easton's Syrup*.—Contains 1 gr. ferrous phosphate, or $\frac{1}{2}$ gr. iron, $\frac{1}{4}$ gr.

quinine sulphate, $\frac{1}{6}$ gr. strychnine hydrochlor. in 60 ms. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

FERRUM REDACTUM

Reduced Iron. (Ferr. Redact.)

Source.—Obtained by the action of hydrogen on ferric oxide. Contains not less than 80 p.c. of metallic iron, or about 8 grs. of metallic iron in 10 grs.

Characters. A fine, greyish-black powder, free from metallic lustre, and from gritty particles. *Insoluble* in water, and in alcohol (90 p.c.), freely soluble in dilute hydrochloric acid

B.P. Dose. 1 to 10 grs. or 0.06 to 0.6 grm.

Iron salts group themselves into three classes:—(1) Ferrous or Protosalts based upon Ferrous Oxide FeO , (2) Ferric or Persalts (sesquisalts) upon Ferric Oxide Fe_2O_3 , and (3) Scale Preparations. Ferrous salts soon become ferric from the absorption of atmospheric oxygen, especially in the presence of oxidising agents, as chlorine, nitric acid, etc.

1. FERROUS SALTS

FERRI CARBONAS SACCHARATUS

(Ferr. Carb. Sacch.)

Saccharated Iron Carbonate

Source. Dissolve 150 grm. liquid glucose in 3000 mils of water and add ferrous sulphate 1000 grm., add this to a solution of sodium carbonate 1078 grm. in 1500 mils of water. Allow precipitate to form, wash with distilled water. Mix liquid glucose 157 grm., dry at 100 °C. Powder the product. Contains not less than 50 p.c. ferrous carbonate, or $7\frac{1}{2}$ grs. of iron in 30 grs.

Characters. An olive-brown, slightly hygroscopic powder; taste, feebly chalybeate. Partially *soluble* in water, soluble with effervescence in dilute hydrochloric acid.

Incompatibles.—Vegetable astringents, acids and acid salts.

B.P. Dose. 10 to 30 grs. or 0.6 to 2 grm.

NON-OFFICIAL PREPARATION

1. *Massa Ferri Carbonatis*, U.S.P. *Syn.*—*Vallet's Mass*—Ferrous sulphate 100; monohydrated sodium carbonate 46; honey 38; sucrose 25; syrup and water, each *q. s.* to 100. Contains not less than 36 to 41 p.c. ferrous carbonate. *Dose*, U.S.P.—4 grs. or 0.25 grm

FERRI SUBCHLORIDUM CITRATUM

(Ferr. Subchlorid. Cit.)

Citrated Ferrous Chloride

Source. Prepared by heating a mixture of equal volumes of hydrochloric acid and distilled water with an excess of iron, until the reaction ceases. Add citric acid one-tenth of the weight of ferrous chloride present. Contains not less than 68 p.c. of ferrous iron (FeCl_2), and not more than 5.8 p.c. of ferric iron (FeCl_3). Contains in 5 gr. about $1\frac{1}{2}$ gr. of iron.

Characters. A buff-coloured powder; taste, acid, metallic and astringent. Almost completely soluble in 1 part of water; readily in dilute mineral acids.

B.P. Dose. 3 to 5 grs. or 0.2 to 0.3 grm.

FE I SULPHAS

(Ferr. Sulph.)

Ferrous Sulphate. $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ Syn. I.V.—*Hirakas*, Beng. *Hira Kasus*, Hind.

Source.—Prepared by the action of diluted sulphuric acid upon iron. Contains not less than 99 p.c. of ferrous sulphate.

Characters.—Transparent green crystals; or a pale bluish-green powder; metallic, astringent taste. *Solubility*.—1 in $1\frac{1}{2}$ of water.

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

OFFICIAL PREPARATIONS

1. **Ferri Sulphas Exsiccatus**—Ferrous sulphate deprived of part of its water of crystallisation by drying at a temperature of 40°C . Contains not less than 80 p.c. FeSO_4 . 3 grs. contain about 1 gr. of iron. A greyish-white powder, slowly but completely soluble in boiled and cooled water. B.P. Dose.— $\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm

2. **Pilula Ferri Carbonatis**. Syn.—*Bland's Pill*; *Pilula Ferri*.—20 p.c. ferrous carbonate, or 3 grs. of iron in 30 grs. B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.

3. **Pilula Aloes et Ferri**.—Contains $\frac{1}{2}$ gr. of exsiccated ferrous sulph. or about $\frac{1}{2}$ gr of iron in 8 grs. B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.

NON-OFFICIAL PREPARATIONS

1. **Magma Ferri Hydroxidi**, U.S.P. Syn.—*Ferri Hydroxidum c Magnesi Oxido*, U.S.P., *Arsenic Antidote*.—Solution of ferric sulphate 40 c.c., mag. oxide 10 grms, water $q\ s$ to 1000 c.c. Dose, U.S.P.—4 oz or 120 c.c

2. **Mistura Ferri Composita**. Syn.—*Griffith's Mixture*.—Ferrous sulph. 6 grm, pot carb 8 grm, myrrh, gum acacia, glucose, each 15 grm, sp nutmeg 10 mls, rose water $q\ s$ 1000 mls. Dose— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

2. FERRIC SALTS

LI QOR FE I PE CHLORI I

(Liq. Ferr. Perchlor.)

Solution of Ferric Chloride

Source.—Obtained by the oxidation of ferrous chloride, prepared by the interaction of diluted hydrochloric acid and iron. Contains 15 p.c. w/v of FeCl_3 , or about $2\frac{1}{2}$ grs. of ferric chloride, or $\frac{1}{2}$ gr. of iron in 15 ms.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 ml.

NON-OFFICIAL PREPARATION

1. **Liquor Ferri et Ammonii Acetatis**. Syn.—*Basham's Mixture*.—Tinct ferr. perchlor 4, acid acetic dil 6, liquor ammon acetatis 50, aromatic elixir 12; glycerin 12, water $q\ s$ to 100. Dose— $\frac{1}{2}$ oz or 15 mls

3. SCALE PREPARATIONS

FE I ET A NII CITRAS

(Ferr. et Ammon. Cit.)

Iron and Amonium Citrate

Source.—Prepared by saturating a warm aqueous solution of citric acid with freshly precipitated ferric hydroxide, adding a slight excess of solution of ammonia, evaporating, and drying on glass plates at 40°C . Contains 20.5 to 22.5 p.c. iron, or about 8 grs. of iron in 40 grs.

Characters.—Thin, dark-red, transparent scales; taste, astringent, deliquescent in moist air. *Soluble* in 0.5 part of water; almost insoluble in alcohol (90 p.c.).

B.P. Dose.—20 to 40 grs. or 1.3 to 2.6 grm.

OFFICIAL PREPARATION

1. **Injectio Ferri.**—Contains $\frac{1}{10}$ gr. iron, or $\frac{1}{2}$ gr. iron and ammonium citrate in 30 ms. **B.P. Dose.**—15 to 30 ms. or 1 to 2 mils.

FERRI ET QUININAE CITRAS

(Ferr. et Quinin. Cit.)

Iron and Quinine Citrate

Source.—Prepared by dissolving freshly precipitated ferric hydroxide and quinine in a warm aqueous solution of citric acid, adding a solution of ammonia, evaporating and drying on glass slides at 40 C. Thin, greenish-yellow scales of a bitter taste. *Soluble* in 0.5 parts of water. Contains 14.5 to 15.5 p.c. anhydrous quinine, and 12 to 14 p.c. iron, or 2 grs. of iron and $2\frac{1}{2}$ grs. of quinine in 15 grs.

Incompatibles.—Alkalies and their carbonates, tannin, vegetable astringents, potassium citrate.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

ADDITIONAL NON-OFFICIAL PREPARATIONS AND DERIVATIVES OF IRON

1. **Ferri Iodidum**—Steel grey or reddish-brown crystalline, hygroscopic masses. *Soluble* in water. *Dose.*—1 to 5 grs. or 0.06 to 0.3 grm.

2. **Ferri et Potassii Tartras.** *Syn.*—*Ferrum Tartaratum.*—In transparent, garnet coloured scale. *Soluble* in water. *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

3. **Ferri Lactas.**—In greenish-white crystals, *soluble* 1 in 40 of water. Readily assimilated. One of the least astringent forms of iron. *Dose.*—1 to 5 grs. or 0.06 to 0.3 grm.

4. **Liquor Ferri Hypophosphitis, B.P.C.**—Solution of ferric sulph. 14.20, solution of ammonia 23; citric acid 7.60, sodium hypophosph. 9.60; sod. citrate 6.60; water q.s., stronger chloroform water to 100. *Dose.*—10 to 30 ms. or 0.6 to 2 mils. (One part of this to 5 of Syrup makes **Syrupus Ferri Hypophosphitis, B.P.C.**—*Dose.*— $\frac{1}{2}$ to 2 drs. or 2 to 8 mils.)

5. **Syrupus Hypophosphitum Compositus, B.P.C.**— $\frac{1}{100}$ gr. of strychnine, $\frac{1}{8}$ gr. of quinine, $\frac{1}{2}$ gr. cal. hypophosph. and $\frac{1}{4}$ gr. each of manganese and pot. hypophosph. in 1 dr. *Dose.*—1 to 2 drs. or 4 to 8 mils.

6. **Injectio Ferri et Arseni, B.P.C.** *Syn.*—*Injection of Iron and Arsenic.*—Strong solution of ferric chloride, 1.75 mil.; citric acid, 2.0 grm.; arsenic trioxide, 0.13 grm.; dilute solution of ammonia, q.s.; sterile water to 100 mil. Contains about $\frac{1}{100}$ gr. of arsenic trioxide in 15 ms. *Dose.*—8 to 15 ms. or 0.5 to 1 ml intra-muscularly.

7. **Ferri, Quininæ et Strychninæ Citras.** In thin, transparent, deliquescent, greenish or golden-yellow scales with an intensely bitter and ferruginous taste. Contains about 15 p.c. quinine, 1 p.c. strychnine, and 13 p.c. Fe. *Soluble* 1 in 2 of water. *Dose.*—2 to 5 grs. or 0.12 to 0.3 grm.

PHARMACOLOGY

Externally.—Iron salts have no action on the unbroken skin, and are not absorbed by it. Ferrous and organic salts are feebly astringent. A solution of ferric salts when applied to a denuded surface, mucous membrane, sores or ulcers coagulates the albuminous secretion, as well as the albumin of the tissues. It also coagulates blood and plasma. The circulation of the part is greatly reduced by the compression

of the coagulated albumin from outside and not by the contraction of the muscular fibres of the walls of the blood-vessels. If there is any hæmorrhage, it is readily arrested by (1) the compression of the blood-vessels from without, and (2) the plugging of the bleeding vessels by the clotting of the blood within them. Therefore it is a powerful **styptic**. It acts as an astringent or irritant according to the concentration used; the irritant effect being due to the acid ion and not to the metal. Iron however has no specific poisonous action on living matter like mercury or antimony. The perchloride, the pernitate and the persulphate of iron are all strong local astringents.

Internally **Mouth**—Iron blackens the teeth and the tongue, from the deposition of iron tannate or sulphide. This is supposed to be due to tannic acid of the food precipitating black tannate of iron, or to the sulphide of iron formed by the action of hydrogen sulphide present in carious tooth. It has a styptic taste, and the ferric salts have a similar action here as on the raw skin.

Stomach.—All iron preparations, in whatever form they are taken by the mouth, are mostly converted into chlorides in the stomach, and not into an albuminate. Even an albuminate is decomposed into a chloride. If given in large doses, or if continued for a long time, all iron salts set up irritation, pain, nausea and vomiting. Prolonged use of inorganic salts is often followed by indigestion and constipation, due no doubt to the astringent action on the alimentary canal. In the presence of gastric secretion and in the presence of easily oxidisable substances, ferric ions are reduced to ferrous. In fact all iron salts are transformed into simple ferrous compounds before they are absorbed by the duodenum and upper part of the intestine; an acid condition of the duodenum favours absorption while alkalinity retards it. The scale preparations however do not ionise in the stomach and therefore do not impair digestion.

Intestine.—In the intestine the ferrous compounds coming in contact with alkaline secretions are converted into insoluble phosphates, carbonates or other complex salts which are not so easily absorbed, the unabsorbed portion being converted lower down into sulphides and tannates by the sulphuretted hydrogen and tannic acid, the latter being derived from the vegetable food, and are passed out with the fæces which are coloured black. The astringent effect is continued in the intestine, and if the dose is large, or continued over prolonged period, iron salts cause constipation.

Absorption—In order to understand the absorption of iron it is necessary to distinguish between inorganic and organic compounds. In the inorganic salts the iron exists in the ionic form, while in the organic compounds the metal

exists in the non-ionisable state. In the various double salts containing citric and tartaric acids, the iron though exists in the non-dissociable form is easily dissociated. The food iron is exclusively organic iron and exists in combination with nucleo-proteins. Plants contain iron in the organic form and take it up from the soil, where it is necessary for the formation of chlorophyll, although it is not actually contained in it as it exists in the hæmoglobin. All vegetable foods therefore contain iron.

Iron is absorbed mainly from the duodenum and to a less extent from the jejunum. Its absorption is difficult and it is generally held that the food iron is absorbed by the gastrointestinal canal, for the growing child derives all the iron necessary for its growth and development from its food. But there was a good deal of controversy regarding the absorption of inorganic iron. All recent experiments however go to prove that inorganic iron can readily be absorbed, and the opinion is gaining ground that even the food iron requires to be broken down into more diffusible ionised form before it can be absorbed by the alimentary canal. All iron compounds are probably absorbed as ferrous ions by the intestinal epithelium and transferred to the white corpuscle of the blood, which convey them to the liver, where they are deposited and gradually elaborated into more or less complex indissociable compounds, one of which is *Ferratin*. The liver must be regarded not only as the storehouse for iron, but as a place where iron is worked up into complex ferruginous organic compounds. These iron granules generally pass into the blood-stream and are utilised by the red bone marrow for the formation of hæmoglobin. The reticulo-endothelial cells have some share in iron metabolism and utilise the iron from degenerated red cells and hæmoglobin for the formation of fresh red cells (*see* page 441). As has been pointed out iron salts coming in contact with the alkaline secretion in the lower part of the intestine are converted into insoluble phosphates, carbonates or other complex compounds which are not easily absorbed. What actually helps the absorption of iron is not clearly understood, and it has been suggested that the vital activity of the intestinal epithelial cells may to some extent have a share in the absorption. It is possible that there is some mechanism governing the absorption according to the requirements of the body, for it has been pointed out by Cloetta that when iron is deficient in food the body has the power of conserving it and utilising every trace of iron in the food, on the other hand when there is excess of iron the intestine ceases to absorb more than is required for the body.

In fact iron is stored up in the liver, spleen and bone-marrow even when injected intravenously and is subsequently excreted by the cæcum and colon. Given orally, iron may

be excreted directly with the stool, or may pass through the portal circulation, absorbed into the system and retained in the liver to be subsequently excreted in the large bowel and passed out with the faeces in an organic form. The process of absorption and excretion is slow, and therefore it has been possible to trace its presence in the liver and estimate the quantity. This is done by feeding some young animals of the same litter with rice and milk only, and another lot with iron in addition to milk and rice as controls. The animals not receiving iron thrive badly and become emaciated, while those receiving extra iron show more iron in the liver. Again if an animal is given a meal containing iron and after some time it is killed and parts of the alimentary canal are hardened, the duodenum and the upper part of jejunum and rectum will show under the microscope distinct evidence of iron (either prussian blue or black granules according to stain used) in process of absorption and excretion. These granules can be traced to the mesenteric glands, the spleen, and to a less extent the liver and the cortex of the kidney. If, however, the animal is allowed to live longer, more granules will be found in the liver and less in the duodenum, spleen and lymphatic glands, showing that the iron has left the spleen and migrated to the liver again to be excreted *via* the large intestine and the caecum. Lastly it has been found that if an animal is treated with iron in whom colotomy has been performed and the lower part of the intestine is daily washed out and the washings examined, a small amount of iron will be found in the lower bowel, where it can only arrive by a process of absorption and elimination.

Older views regarding the absorption of iron are of historical interest. Buchheim held that inorganic iron was not absorbed but improved anæmia by stimulating appetite and digestion and the extra food taken supplied the necessary iron to reconstitute the blood. Bunge held a similar view. He argued that in anæmia digestion was greatly disturbed and alkaline sulphides were formed which combined with the food iron to form Fe_2S_3 , which was an inorganic salt and therefore incapable of absorption. When iron was given in these conditions it combined with the alkaline sulphides leaving the organic iron to be absorbed. But mere stimulation of appetite and digestion by other tonics does not improve anæmia and that sulphides of iron which do not combine with alkaline sulphides cure anæmia. These views therefore are not accepted and the modern view of the absorption of iron has been given above.

Recently the idea has been put forward that the formation of hæmoglobin is helped by the presence of minute quantities of copper in addition to iron which acts as a catalytic agent. Moreover a copper free iron salt fails to improve induced anæmia of rats. It has been estimated that the blood of man contains on an average 0.132 mg. of copper per litre, of which 50 p.c. exists in hæmoglobin. In conjunction with copper manganese enhances the catalytic action of copper.

Blood.—Iron is an essential constituent of every cell in the body and the normal process of cell oxidation depends upon its presence. About two-thirds of the iron in the body exists in the form of haemoglobin. Its production therefore is intimately associated with iron metabolism. An adult man contains about 3.0 to 3.5 grms. of iron, of which about 2.4 to 2.7 grms. are in the form of haemoglobin. About 20 mg. is excreted daily on a normal diet, and this loss is replaced by the iron of the food, and a minimum of 6 to 12 mg. is required to maintain this equilibrium. The iron content in different foods varies however. In health, iron has very little effect upon either the quantity or the quality of the blood-corpuscles, but increases the reserve iron, so that its transformation into haemoglobin occurs only as required by the body. But in anemia both the number of corpuscles and their haemoglobin value are markedly increased. Since patients suffering from chlorosis do not improve with foods containing iron, in fact chlorosis appears in persons amply supplied with food iron, but improves under inorganic iron, it has been suggested that iron acts as a chemical stimulus to the blood-forming organs, and not being an entirely foreign constituent is less injurious to the body than other stimulants. This view however has been challenged, and it has been argued that in animals rendered anemic recovery is not accelerated by food iron as would happen if the blood-forming organs are actually stimulated by iron (Zahn). It has therefore been suggested that improvement is due to the abundance of the material supplied to the blood-forming organs. The fact remains that iron is a valuable hematonic.

Metabolism.—With the improvement of the red blood-corpuscles there is necessarily an increased absorption of oxygen, and an increased oxidation of tissues. Hence, the functional activity of all the organs of the body is stimulated, leading to the general improvement of the tone of the body. Iron is therefore a most valuable **general tonic**. As the whole system shares in the benefit, the menstrual flow, if it had been stopped, is re-established and many disordered functions are rectified. Although these results are mainly indirect, depending upon the improvement of the blood, it should be remembered that iron is a constituent of all cells and some effects must be direct.

Excretion.—Iron salts are feebly excreted by the renal cells, and their estimation is difficult, while some found as much as 8 mg. daily, others estimated it less. It is excreted in largest quantity through the bowels, mainly the large intestine. The ferric salts slightly diminish the secretion of urine, while the other preparations have no effect, except the tartrate and the acetate, which slightly increase it. They may sometimes irritate the bladder, and may cause nocturnal incontinence of urine in children.

THERAPEUTICS

Externally.—Organic iron salts and ferrous salts, except the sulphate, are not locally used. Though iron salts are powerful astringents and styptics they are not much used nowadays as they cause a dirty coagulum and irritation of the tissues. The solution of perchloride mixed with equal quantity of glycerin is used as a paint for its astringent action in different conditions of the throat and tonsils, viz. enlarged tonsils, diphtheria and sore-throat. The same may be used as a gargle well diluted. A solution of ferrous sulphate (10 grs. to 1 oz. of water) is an extremely useful local application in erysipelas, but its stain on the linen is not removed by washing. Sometimes the solution of perchloride may be painted for the same purpose. Ferrous sulphate or copperas has been used as a disinfectant for cesspits, water closets, etc. It acts by precipitating the proteins which mechanically carry down the bacteria.

Internally. Gastro-intestinal tract.—Because of the astringent effect on the intestine, iron salts, specially the ferric compounds, are used in diarrhœa. Chronic diarrhœa, rebellious to all manner of treatment, is sometimes wonderfully checked by the solution of perntrate (5-15 ms.). It is specially useful in those cases where the patient is anæmic. Here it acts not only as an astringent but by improving the condition of the blood gives tone to the intestine. Chronic constipation may often be successfully removed by ferrous sulphate and extract of nux vomica or extract of belladonna. Humid peroxide of iron is an antidote to arsenical poisoning. It can be prepared fresh by mixing a solution of perchloride of iron 3 ozs., with bicarbonate of soda 1 oz. in solution; half an ounce of this is given every 5 or 10 minutes. Magma Ferri Hydroxidi, U.S.P. may be given in its stead in one ounce doses diluted. An enema of the solution of perchloride of iron (60 ms. in 1 pint of water) kills thread worm.

Blood.—Iron is a valuable remedy in anæmia. The forms of anæmia which respond to iron treatment are those characterised by small size and pallor of the red cells, pallor or hypochromia due to deficient corpuscular content of iron and hæmoglobin. Iron salts are therefore extensively used in chlorosis, scrofula, chronic nephritis, convalescence from acute and chronic illness, etc. Ferrous salts are the most potent preparations and most of the idiopathic microcytic anæmias are cured by these salts. Some cases are however refractory and do not respond to iron. This refractoriness is often due to deficient absorption from the intestine.

Anæmia and Chlorosis.—Ordinary forms of anæmia traceable to some definite cause such as scurvy, malaria, protracted hæmorrhage, lead poisoning and ankylostomiasis, etc., are materially benefited by a course of iron, as well as by the removal of the cause.

Iron is the most valuable remedy in chlorosis. Although the actual amount of food iron is not deficient in this disease, chlorotic patients are not able to assimilate enough iron from the food; moreover owing to poor appetite and digestion, the quantity becomes still less and the body soon becomes depleted of iron causing anæmia with deficiency of hæmoglobin. There is therefore deficient supply of oxygen for the body requirements as evidenced by breathlessness, cardiac weakness and œdema. Iron by improving the condition of hæmoglobin brings on an improvement in the patient's condition. Insoluble preparations being less irritating to the stomach are tolerated better, and therefore Bland's pill, reduced iron and saccharated iron are largely used. The scale preparations may be used in the form of mixture with equally good results. Constipation often gives trouble in this disease and is increased by the use of iron; aloe and belladonna with pill, and magnesium sulphate with mixture answer the purpose well.

In anæmia due to blood loss, recovery generally follows without any use of iron, as the reserve store of iron is called upon to replace this loss. But recovery is hastened by the administration of iron to increase the reserve store of iron.

If the anæmia is due to malaria, ferr. et quinin. citras, or Easton's syrup may be given with advantage. The same preparations may also be employed as a tonic during convalescence after an acute febrile attack or any other protracted illness.*

Splenic anæmia.—Davidson† has pointed out that although it is said that iron is of little value in this form of anæmia, it has given excellent results in this condition. He is of opinion that the three common causes of hypochromic anæmia are frequently present in this condition, *viz.* (a) defective intake of iron through poor diet; (b) deficient absorption of iron from the presence of achlorhydria; and (c) increased demand of iron from blood loss.

Pernicious anæmia.—Since this form of anæmia arises from the deficiency of the specific anti-anæmic factor contained in the liver, iron is of little value in this condition. Beebe and Lewis‡ consider iron as an important adjuvant to liver therapy, specially in cases where there is deficiency of the anti-anæmic factor derived from the protein with deficiency of iron assimilation. Pernicious anæmia when treated with whole liver does not as a rule require iron as this organ is particularly rich in that metal. Since the introduction of

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Ferr. of quinin. cit	gr. 10	; <i>Lancet</i> , Sept. 1931.
Acid. hydrochlor. dil.	ms. 10	† <i>American Journal of Medical Science</i> , 1931.
Liq. strych. hydrochlor.	ms. 3	
Sp. chlorof.	ms. 10	
Aqua	ad oz. 1	

the parenteral method of treatment of this disease the position has changed, as the anti-anæmic fraction does not contain any iron which is given as injection and in consequence the body's reserve store of iron is rapidly utilised in order to supply the large requirement of the hæmoglobin synthesis which occurs during recovery. It is therefore necessary that iron should be given during the relapse stage of pernicious anæmia. And it has been found that there is a marked acceleration in the speed of recovery, both in the hæmoglobin level and in the patient's physical condition by giving 60 to 90 gr of iron and ammonium citrate daily.

Many conditions depending on anæmia, and which are sometimes more troublesome, are benefited by a course of iron. Thus *amenorrhœa* when due to anæmia often yields to iron specially when given in combination with aloes, as Bland's pill and pil. aloes et ferri. Similarly gastric catarrh and œdema so common in profound anæmia, also disappear with the exhibition of iron. These effects are due to improvement of hæmoglobin which follows the use of iron and not to any special action either on the stomach or the circulation. Iron being an integral part of all cells of the body, it is possible that it helps to perform their function better when there is an abundant supply of this element, therefore iron is a valuable tonic.

Bright's disease.—Acetate of iron is a valuable remedy in this disease. It not only improves the blood, but lessens or removes the albumin. Basham's mixture is a very useful preparation in chronic parenchymatous nephritis.

Scrofula and other tubercular affections are benefited by a course of iodide of iron.

Iron is useful in certain septic conditions due to streptococcal infection. The solution of perchloride is used in erysipelas, puerperal sepsis, acute tonsillitis and in other bad forms of sore-throat such as hospital sore-throat, with very good results. In these cases it is usually combined with quinine. It is also used in diphtheria.

Nervous system.—Iron cannot directly influence the nervous system, but indirectly it does by improving the nutrition and the general functions of the bodily organs. Easton's syrup, syrupus hypophosph. co., syrupus ferri hypophosph. may be selected with advantage.

Caution.—The following points should always be remembered during the administration of iron :—

1. Iron sometimes irritates the stomach even of healthy persons.
2. Begin with one of the milder preparations and give it after meals.
3. Use it very cautiously in plethoric subjects, or in those who are predisposed to apoplexy.

4. Change your preparation from time to time during a long course of iron treatment, or stop it at intervals.

5. If iron causes constipation, combine it with purgatives.

6. If iron causes headache or indigestion, stop it at once.

Prescribing hints.—The choice of a preparation sometimes becomes difficult to a young practitioner. We have metallic iron, ferrous salts, ferric salts and the scale preparations. The student should distinguish an astringent from a non-astringent preparation and should bear in mind that there are a few, such as the iodide, arsenate, the phosphate and the citrate with quinine, whose value depends mainly or to some extent, upon the other ingredients they contain. The organic salts are non-astringent, but they have not proved so effective as the inorganic ones, as the larger molecules of these have to be broken down by the digestive juices before they can be absorbed. Of the inorganic salts the ferric salts are more astringent than the ferrous salts. Although both the organic and inorganic compounds are absorbed and produce their therapeutic effects, the ionised iron is more active therapeutically. All iron preparations should be given after meals, except reduced iron, which should be given before meals to enable the gastric juice to act upon it. Reduced iron does not impair digestion, but to be effective should be given in massive doses. The scale preparations are very effective preparations since they do not oxidise in solution nor irritate the stomach. They can be given in large doses, i.e. 15 to 20 grs. per dose, three times a day. The insoluble ferrous compounds like the Bland's pill or *ferri carbonas saccharatus* are largely used, the latter preparation being very useful for children. Bland's pill however becomes converted into ferric salt and too hard when kept long and passes through the intestine unchanged. The perchloride is considered by some as the best preparation for treatment of anaemia. But clinical experience has shown that ferrous salts act better, possibly because they are less astringent and irritant, and are less liable to impair digestion or cause constipation. In fact the opinion is gaining ground that even ferric salts require to be reduced to ferrous compound before they can be absorbed.

Since large doses of iron are required for the cure of anaemia, it is evident that the absorption of iron, when given by the mouth, must be very poor. Iron is therefore used parenterally either as *injectio ferri* or in combination with arsenic, as *injectio ferri et arseni*. Heath, Strauss and Castle* found that 32 mg. of metallic iron when injected was approximately equal, from the point of view of blood-building, to 1000 mg. of iron by mouth (90 gr. of iron and ammonium citrate). But inasmuch as the optimal parenteral

* Journal of Clinical Investigation, 1932, 11

dose is very near the toxic dose, the above authors recommend that in the routine treatment iron should be given by the mouth. Except in the treatment of nutritional anæmia of milk-fed infants, copper is not regarded as an adjunct in the treatment of all forms of hypochromic anæmia. Being toxic when given intravenously, iron should never be used by this route.

The perchloride is largely employed in various ways, as a gargle, pigment, spray, dressing (*e.g.* cotton or lint soaked in solution 15 p.c.), rectal or urethral injection, or mixture. If given in a mixture, glycerin or lemon juice covers the ferruginous taste. The infusion of quassia, calumba or chiretta may be used as a vehicle as they do not contain tannin. The constipating property of iron salts is best removed by magnesium sulphate, if given in a mixture; or by aloes or rhubarb if in pill. The inky colour which results if they are combined with cinchona or digitalis, is cleared by the addition of a few drops of diluted phosphoric acid. The action of iron is not affected by this chemical change. By addition of alkali the acid reaction of the iron salts and their astringency are lessened, and therefore Bland's pill and Griffith's mixture are so well-borne. Syrupus Ferri Phosphatis and Syrupus Ferri Iodidi should be given alone diluted. When prescribed with acids, syr. ferr. iod. liberates iodine and with alkalis will throw down insoluble iron compounds. Ferrous sulphate and citrated ferrous chloride are best given in solution but they are more astringent. To prevent blackening of the teeth, iron mixture should be swallowed through a glass tube or a quill. Inj. ferri, arsenite of iron, or ferri cacodylas are largely used hypodermically. Parrish's chemical food is an excellent preparation for children and delicate women. Citrate of iron and quinine should not be mixed with alkalies or alkaline carbonates as the quinine is precipitated.

GROUP XXIV

DRUGS ACTING ON THE SKIN

The skin is one of the most important organs of the body performing diverse functions. It protects the underlying structures, regulates body temperature by variations in the blood supply and sweat formation, and plays an important part in the general metabolism by absorbing the ultra-violet rays and utilising them in the formation of vitamin D so important for growth and nutrition. Being a highly differentiated tissue and being freely supplied with sensory nerves, it reflexly affects respiration and circulation, and any injury to the skin is followed by local and general effects depending upon the nature and intensity of the damages (*see counter-irritants*, page 644). Thus symptoms of poisoning and shock following extensive injury to the skin, as happens after

burns, are attributed to the absorption of the break-down products of histamine-like substances. Skin rash is a common accompaniment of many poisons and infections, and it is possible that it plays an important part in the defensive reactions that protect the body from microbial invasion.

Sweat.—Secretion of sweat is an important function of the skin and is performed by the sweat glands. Although an excretion, inasmuch as it helps elimination of water, salts and nitrogenous end products, it regulates the body temperature by the evaporation of the water. The total amount of water lost in 24 hours is about 500 to 700 c.c. and may be greater under special circumstances. The reaction of human sweat is acid, due to the presence of fatty acids derived from the sebaceous glands. The secretion of sweat differs from the urine in that it is influenced by nerves and is independent of blood-pressure or general circulation; in fact there is abundant sweat when the skin circulation is almost nil, as for instance, the cold sweat and death sweat; although increase of blood volume, as happens after drinking large quantities of water, is followed by diaphoresis.

The sweat glands are supplied by the sympathetic and are also under the control of the central nervous system. Pharmacologically the peripheral mechanism of the sweat glands acts as if they are innervated by the parasympathetic, *i.e.* the nerves are cholinergic. Adrenaline, which stimulates sympathetic, produces no effect on sweat secretion. Mayer and Gottlieb hold that the sweat glands receive in general augmentor nerves from both the autonomic systems, and that in man and certain animals only the parasympathetic endings are accessible to the action of drugs.

Drugs that increase the secretion of sweat are called **diaphoretics** or **sudorifics**. They act as follows:—

1. *By directly stimulating the centre.*—Drugs which stimulate the spinal centres also stimulate the spinal sweat centres. The following drugs stimulate the centre and cause diaphoresis; they are ammonium acetate, ammonium citrate, and camphor. The centre is also stimulated by venous blood.

2. *By stimulating the nerve-endings.*—Pilocarpine is most powerful in this respect. Physostigmine, acetyl-choline and muscarine act similarly.

3. *By dilating the cutaneous vessels.*—As by local heat, hot baths, turkish baths, hot drinks, or by drugs which specifically dilate vessels of the skin, as alcohol, opium (Dover's powder), chloral hydrate, salicylates, acetanilide, etc.

4. *Reflex stimulation of the centre.*—Stimulation of the throat and stomach, as by tickling the throat or by the use of emetics, such as antimony and ipecacuanha, will produce perspiration through reflex stimulation. Other examples of this are sweating in nausea and during psychological stimulation of the cerebrum, as from fear or anxiety.

Therapeutics.—Diaphoretics are indicated:—

- (a) To reduce pyrexia.
- (b) To cut short a threatening catarrh or inflammation caused by specific poisons or metabolic products.
- (c) To lessen the accumulation of fluid in the system, as in dropsy, and to relieve excretory organs, *e.g.* kidneys in albuminuria.
- (d) To eliminate excrementitious products through the skin when the action of the kidneys is suspended, as in uræmia. Pilocarpine is most useful for this purpose.
- (e) To promote cutaneous circulation in many chronic skin diseases, *e.g.* warm water or Turkish baths in psoriasis.

Drugs which diminish the sweat are known as **anhidrotics**. They may act as follows:—

1. *By depressing the ends of the secretory nerves (parasympathetic).* The effect of atropine is most powerful.
2. *By lessening the activity of the sensory nerves,* as by cold application, cool atmosphere, etc.

Some drugs like acids, quinine, *nux vomica* are also used but their mode of action is not known.

Drugs that affect the hair.—The hairs are epidermal growths contained in pits or hair-follicles. Except certain parts, the whole body surface is covered with hairs. But the growth of hair on the scalp, face, axillæ and in the regions of the external genitals are controlled in a varying degree by the sex hormones. The pituitary and thyroid glands also influence the growth of hair. The influence of nerves on the growth of hair has not been satisfactorily established.

When baldness is due to defective nutrition as happens after prolonged illness, general tonics and stimulating applications like cantharidin, rosemary, capsicum, quinine and pilocarpine in the form of lotions are useful. When due to metabolic disturbance, the use of drugs to supply the deficient internal secretion like thyroid or pituitary is indicated.

Depilatories are drugs used to remove hairs. These may be (a) *local*, and the effects depend upon the presence of a sulphide and an alkali. The freshly prepared paste is applied in a thick layer over the part and allowed to remain for 5 to 10 minutes and then scraped off with a blunt knife, and cold cream applied to the inflamed skin. Barium sulphide (*see* page 108) is largely used for the purpose. It dissolves the hair shafts and causes them to break off leaving the skin quite clean and bald; (b) *internal*, *e.g.* thallium (*see* page 135).

CLASS A: Irritants and Counter-irritants

These are drugs or measures which relieve inflammation or congestion of some internal organs by producing local irritation. The use of irritants for various purposes is one

of remote antiquity, but the method of doing this has not always been the same, yet burning with hot iron, cautery, application of blisters and the use of irritant plants to produce local irritation or inflammation are still to be found. The principle however remains, and instead of the violent methods milder remedies are now used.

All these drugs act by stimulating nerve-endings which produce (1) local vaso-dilatation and inflammation due to axon reflexes; (2) vaso-dilatation of distant organs due to axon reflexes acting through the posterior root; and (3) medullary reflexes affecting respiration and circulation (Clark).

The effects of counter-irritation are local, general and remote. The local effects may be mild being limited to production of congestion and redness of the skin, *i.e.* rubefaction, and the drugs producing these effects are known as **rubefacients**. In this stage there is arterial and capillary congestion, at first active, later passive, and is usually accompanied by sensory stimulation with itching, burning and pain. These effects are axon reflexes, *i.e.* the vaso-dilatation with all its accompaniments occurs without the impulses passing through a nerve cell. The condition of the skin returns to normal without leaving any local lesion. If the irritation is too strong, or if the irritant is allowed to remain for a longer period, little vesicles appear, which eventually coalesce and form one large blister, and the drug producing this effect is known as **vesicant**. In both these conditions exudation occurs, but when the exudate is greater than can be removed by the lymphatics, it collects forming a blister. If the application is mild or not continued long the effects following application of rubefacients or vesicants resemble those of local inflammation. If the irritation is very severe and the irritant does not penetrate the epidermis but only the cutaneous glands, pustules form, which are at first discrete but later become confluent, and drugs which produce these effects are known as **pustulants**, *e.g.* tartar emetic and croton oil. **Caustics** or **escharotics** destroy the vitality of the part on which they are applied. They cause sloughing and inflammation of the surrounding area, *e.g.* zinc chloride, potassium or sodium hydroxide.

Apart from local effects the drugs of this group produce certain general changes, due to reflex stimulation of the vital medullary centres, *viz.* the cardiac, vaso-motor and respiratory. The results are not uniform and depend upon the intensity of the irritation produced. A mild irritation accelerates the heart and raises the blood-pressure; while a more powerful irritation slows the heart through vagus stimulation with fall of pressure through enormous dilatation of the splanchnic vessels. Similarly respiration is stimulated by mild irritation, *e.g.* sinapism, or application of cold douche

on the face in narcotic poisoning, faintness, or hysteria. Owing to the changes in the distribution of the blood through vaso-motor disturbance, the temperature varies. There is leucocytosis specially after the use of vesicants, while the absorption of oxygen and elimination of carbon dioxide are augmented.

The exact manner in which the counter-irritants act and exert their beneficial effects on distant organs is still a matter of dispute. Much light has however been thrown by the work of Head and Mackenzie, who have shown a relationship between the viscera and certain skin areas and body wall through the nervous system. They pointed out that the tenderness of the superficial tissues may be a manifestation of inflammation or injury of one of the internal organs. Thus tenderness of the skin and muscle of the epigastrium implies ulcer of the stomach. In many instances the pain is referred to situations remote from the organs giving rise to it. Thus the pain of biliary colic may be felt in the epigastrium, that of renal colic in the testicle, that of heart affections in the left arm. These tender areas or Head's areas do not correspond to posterior nerve roots but to their segmental relations. According to Head the spinal cord and brain are regular segments, and that a lesion implicating a nerve from a particular segment affects all the nerves whose centres are in that particular segment. It is possible that the good effects which follow application of counter-irritants may be the result of conferred hypersensitiveness to stimuli, to reflex changes in the circulation, or perhaps to psychical effects on the mind.

Therapeutics.—Counter-irritants are indicated as follows:—

(1) To subdue inflammation or to afford relief to the circulation of a part or organ in direct vascular connection with the skin selected for the application of rubefacients or vesicants; *e.g.* the application of a blister in acute pneumonia, pleurisy, hepatitis, etc.

(2) To help absorption of subjacent or subcutaneous morbid growths or effusion, *e.g.* the application of flying blisters in pleuritic effusion and synovitis, and of iodine in enlarged glands.

(3) To relieve pain from neuralgia, *e.g.* sciatica and facial neuralgia.

(4) To allay central nervous irritability, as in hysteria.

(5) To reflexly stimulate the central nervous system; as in syncope, narcotic poisoning.

(6) To relieve muscular irritability, *e.g.* sinapisms in cramps of cholera, and lumbago.

(7) To remove any morbid process from the seat of disease to the irritated surface; as the application of a mustard plaster to the great toe or foot when gout attacks important

organs When counter-irritants act in this manner, they are called *revulsives* or *derivatives*.

CANTHARIDINUM

(Cantharidin.)

(Cantharidin. $C_{10}H_{12}O_4$)

Source.—Obtained from various species of *Cantharis* (Spanish fly), or of *Mylabris*.

Characters.—White glistening crystals; odorless. Very sparingly soluble in water, soluble in about 1100 parts of alcohol (90 p.c.) More soluble in chloroform, acetone and fixed oils.

OFFICIAL PREPARATIONS

1. **Emplastrum Cantharidini.** *Syn.*—*Blistering Plaster*.—0.2 p.c. cantharidin
2. **Liquor Epispasticus.** *Syn.*—*Blistering Liquid*.—0.4 p.c. cantharidin.

PHARMACOLOGY

Externally.—Locally applied to the skin, cantharidin does not show any sign of action until after 2 or 3 hours, when tingling and burning are felt on the part, soon followed by redness; referable to the irritation of the local nerves and the dilatation of the local blood-vessels. Vesicles appear next which run together and form one large bleb. Hence it is an **irritant**, **rubefacient** and **vesicant**, but its action is slower than many others of the same class. Cantharidin is freely absorbed by the skin.

Internally. **Gastro-intestinal canal.**—Unless given in very minute doses well diluted, cantharidin in the form of tincture (dose, 2 to 5 ms.) causes severe irritation of the mouth, fauces, stomach and bowels, producing burning pain in the mouth, throat and abdomen, vomiting and purging. The vomit and the motion may contain blood. Therefore it is a most powerful gastro-intestinal irritant.

Urinary organs.—Cantharidin, absorbed from the skin or stomach and bowels, is slowly excreted by the kidneys, which it stimulates and acts as a diuretic. In large doses it causes pain in the loins, and burning and scalding in the bladder and urethra leading to strangury, albuminuria and hæmaturia. These symptoms are due to active inflammation of the glomeruli, which spreads to the cells of the tubules until all the tubules are involved, and to irritation of the fundus and sphincter of the bladder.

Genital organs.—In poisonous doses it inflames the genital organs and causes violent priapism and numerous seminal emissions. It produces congestion of the uterus and may bring on menstruation or abortion.

Acute toxic action. Besides the irritant effects on the alimentary and genito-urinary tracts already described, it affects the heart, respiration and nervous system producing quickened pulse and respiration, headache, mental confusion, loss of sensibility, convulsion, dyspnoea, and death.

Treatment.—Emetics, pump, mucilaginous drinks, raw eggs. *Oils and fats should be avoided as they increase the solubility of the drug.* Morphine or opium suppository, and sitz bath to relieve strangury.

THERAPEUTICS

Externally.—Therapeutic indications of counter-irritants having been fully described, only some of the specific uses of cantharidin are given below :—

1. *To increase local circulation and thereby promote local nutrition*, cantharidin is used well diluted in the form of hair lotions or hair-oils in the falling off of hair and alopecia.

2. *To relieve pain* of neuralgias, blisters should be applied over the posterior branch of the spinal nerve-trunk close to the spine, for if they are put on the seat of pain, they intensify the suffering. In sciatica they may be used as flying blisters along the course of the nerve. If pain is caused by a localised inflammation, it is relieved by the direct application of a blister over the seat of inflammation, as in acute articular rheumatism.

3. *To promote absorption of morbid products*, blisters may be applied over the joints in chronic rheumatism, synovitis and arthritis; over the chest in pleuritic or pericardial effusions; over the abdomen in subacute peritonitis, ovaritis, pelvic cellulitis, etc

4. *To reduce inflammation*, a blister should be applied a little away from the seat of inflammation, as in pericarditis and pleuritis in thin subjects. Counter-irritation behind the ear or high up on the temple reduces inflammation of the eyes, and on the perineum relieves prostatitis.

5. *To arrest spasm and reflex disturbances*, e.g. blisters over the epigastrium in obstinate vomiting.

Internally.—Cantharidin is only rarely used internally because it is such a powerful irritant.

Caution.—Cantharidin blisters should be avoided or very cautiously applied to children; weak, anæmic and old persons, pregnant women and those who are subject to renal disease, as they may cause strangury. Neither should they be applied to the back of bedridden patients or to paralysed limbs, as they may produce troublesome sores.

Prescribing hints.—To prevent absorption of the cantharidin, the plaster should only be kept on till the vesicles form (about 3 to 5 hours), when a hot poultice will help the rising of a bleb. It is then generally punctured to let out the serum and dressed with cold cream or soft paraffin. Sometimes we apply flying blister, *i.e.* a series of small blisters, each not larger than a shilling or eight anna bit, kept on for about two hours in one spot, then removed and applied a few inches away for two or three hours, and so on until the affected area is covered. Before applying a blister, the skin should be thoroughly washed with soap and water and

rubbed with a towel until the part becomes reddened. The plaster sometimes requires warming before application.

CLASS B: Emollients and Demulcents

Emollients are drugs which soften or relax the skin upon which they are applied. They are bland, oily or fatty substances and prevent cracking of the skin by supplying it with fat or moisture. *Demulcents* are substances of a viscid character which protect mucous membranes from irritation.

Emollients and demulcents are :

Olive Oil, Sesame Oil, Cottonseed Oil, Almond Oil, Linseed Oil, Arachis Oil, Glycerin, Honey, Liquorice, Acacia, Tragacanth, Starch, Soap, Paraffin, Oleic Acid, Lard, Wool Fat, Suet, Beeswax.

OLEUM OLIVAE

Olive Oil. (Ol. Oliv.)

Source.—The oil expressed from the ripe fruit of *Olea europæa*.

Characters. Pale yellow, or greenish-yellow, liquid with faint odour and bland taste. Sp. gr. 0.915 to 0.918.

Composition.—(1) *Olein*, glyceride of oleic acid, 93 p.c.; and (2) *Linolein*, glyceride of linoleic acid, 7 p.c. (3) *Palmitin*, a solid oil composed of palmitic acid and glyceryl. (4) *Arachin*.

B.P. Dose. $\frac{1}{2}$ to 1 oz. or 15 to 30 mils.

OFFICIAL PREPARATION

1. **Unguentum Aquosum.**—Aqua about 24 p.c.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Olive oil being a bland unirritating fixed oil is applied as an excellent emollient in dry skin diseases, such as psoriasis and xeroderma. It forms a basis for liniments and ointment, and as a lubricating agent is employed in massage. It softens and aids the removal of the scabs of eczema, favus, etc. Mixed with 4 or 5 p.c. of phenol, it is applied in the desquamative stage of scarlatina and small-pox. Lin. calcis (lime water 1, olive oil 2) is a soothing protective to burns and scalds. The oil is absorbed by the cutaneous lymphatics, and gives nutrition to the tissues, but not to the same extent as is done by cod-liver oil.

Internally.—As a demulcent, it is useful in irritant poisoning, except by phosphorus. In small doses, it undergoes the same changes in the intestinal canal as cod-liver oil and is absorbed. It is therefore a nutrient and a food, and can be given in wasting diseases. In large doses (1 to 2 ozs.) it lubricates the gut and is a mild laxative, producing painless, soft stools, and is therefore of great value in inflamed and ulcerated piles, rectal ulcers, anal fissures, and constipation, especially if produced by opium. It acts also as a laxative when given as an enema (4 ozs. to $\frac{1}{2}$ pint of starch mucilage), and in faecal impaction and intestinal obstruction (5 to 20 oz.). It is also used as a vehicle for rectal administration of ether and paraldehyde and for the hypodermic administration of ether and camphor.

Because the cholesterine of the gall-stone is soluble in pure olive oil at the normal bodily temperature, it has been recommended as a solvent for gall-stones on the supposition that some of the constituents of the oil are excreted with the bile, but as there is not the slightest evidence that the oil can reach the gall-stone in the gall-bladder or cystic duct its value is doubtful. 10 to 20 oz. or even more of the oil are however given daily to those who suffer from biliary calculi. It reduces the acid secretion of the stomach, and by stimulating the contraction of the gall-bladder acts as an indirect cholagogue. Its use has therefore been advocated in gastric ulcer and in dyspepsia without ulcer, but where the symptoms are similar to those of ulcer. In various disorders of the gall-bladder, such as cholecystitis without stones, cholelithiasis and in atony of the gall bladder its use relieves the symptoms.

It may be administered alone, in capsules or in the form of emulsion.

OL U SESA I

Sesame Oil (Ol. Sesam.)

Syn.—Teel Oil, Gingellı Oil

Source.—The oil expressed from the seeds of *Sesamum indicum*.

Characters.—A pale yellow liquid, faint odour, bland taste. Sp. gr. 0.921 to 0.924.

Composition.—(1) *Sesamin*, a crystalline substance. (2) Liquid fats, 70 p c, consisting of *glycerides of oleic and linoleic acids*. (3) *Sesamol*, a phenol (4) *Solid fats*, 12 to 14 p c, stearin, palmitin, etc.

B P Dose — $\frac{1}{2}$ to 1 oz or 15 to 30 mls.

Uses.—Used as a *substitute for olive oil* to make liniments, ointments and plasters.

OLEU GOSSYPH SE INIS

(Ol. Gossyp. Sem.)

Cottonseed Oil.

Source.—A fixed oil obtained from the seeds of various cultivated species of *Gossypium*.

Characters.—Pale yellow, or yellow, oil. Almost odourless, with a bland taste. Slightly *soluble* in alcohol (90 p c), miscible with ether and chloroform and with light petroleum. If it solidifies it should be gently warmed and thoroughly mixed before use.

Composition.—Glycerides of oleic, linoleic, stearic and palmitic acids.

B P. Dose — $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

Uses.—It is used for the same purposes as olive oil. Being cheap it is preferred to other oils for external use.

OLEU A YG ALAE

Almond Oil. (Ol. Amygdal.)

Syn.—Oleum Amygdalæ Expressum, U S P.

Source.—A fixed oil obtained from the seeds of *Prunus communis* var. *dulcis*, or of *P. communis* var. *amara*.

Characters.—Pale yellow, nearly inodorous, with a bland, nutty taste. Sp. gr. 0.915 to 0.920. *Solubility*—In ether, chloroform, slightly in alcohol (90 p.c.)

Composition.—Chiefly olein and linolein

.B.P. Dose — $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

PHARMACOLOGY AND THERAPEUTICS

Externally.—Almond oil is a demulcent and emollient, and being a bland oil makes a good basis for many hair-oils and ointments. It is a soothing application for chapped hands, excoriations and irritable skin diseases.

Internally.—Sweet almond is nutritive. Its flour being devoid of starch is given to diabetic patients as a substitute for starchy food, the only objection to its use being its high price.

The oil is a mild purgative in 120 to 240 ms. doses. An enema of 1 to 3 pints of the oil is effective in impaction of feces and obstruction of bowels. It is pleasanter than olive oil, but expense limits its use and leads to frequent adulteration.

LINUM

Linseed

Syn. Flax Seed; Lini Semina **Syn. IV**—*Tisi, Mashna*, Beng. *Alsi*, Hind.

Source.—The dried ripe seeds of *Linum usitatissimum*.

Characters.—Small, brown, glossy, nearly flat seeds; 4 to 6 mm. long, ovate, obliquely pointed, glabrous. Internally yellowish white with two oily cotyledons. No odour; taste, mucilaginous, oily. Three varieties are seen, viz. brown, white and red.

Composition.—(1) *Mucilage*, 6 p.c. in the testa. (2) *Pfixed oil (off)*, which consists of *glycerol* combined with linoleic acid, 30 to 40 p.c.

LINUM CONTUSUM

(Crushed Linseed. (Linum Contus))

Syn.—Linseed Meal; Lini Semina Contusa.

Source.—It is linseed reduced to a coarse powder. Should be recently prepared.

Characters. A brownish yellow powder, with visible fragments of brown testa. Odour, bland, not pungent or rancid, when mixed with warm water.

OLEUM LINI

Linseed Oil. (Ol. Lini)

Source and characters.—A yellowish brown oil expressed from linseed. Taste, bland; odour, characteristic. "Boiled" linseed oil should not be used.

B. P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

PHARMACOLOGY AND THERAPEUTICS

Externally.—Contused linseed in the form of a warm poultice is used to disperse threatening local inflammations. It acts by dilating the local blood-vessels and by relaxing the tissues relieves the tension and pain caused by pressure over the periphery of the sensory nerves. But if the poultice is too hot it increases pain and tension. If the leucocytes have already passed through the coats of the vessels, and suppuration has commenced, a warm poultice helps it to reach the surface. Hot linseed meal poultice is an excellent, mild, continuous counter-irritant for deep-seated inflammations, such as pneumonia, bronchitis, broncho-pneumonia,

pericarditis, peritonitis, pelvic cellulitis, etc. The counter-irritant effect can be greatly increased by dusting powdered mustard over the surface of the poultice, or mixing it (1 in 16) with the meal

The oil makes a good emollient application to burns and scalds in the form of carron oil (see page 103). It can also be used as an *enema* (1 lb.) in impacted conditions of the rectum and lower colon.

Internally—Linseed tea, *i.e.* the infusion of linseed, especially when combined with lemon, is a reputed domestic demulcent drink in throat cough. The ordinary formula for linseed tea is linseed $2\frac{1}{2}$ drs., liquorice root 1 dr., boiling water 10 oz., infuse for two hours. This can be taken sweetened with sugar. It has a slightly diuretic action and a patient with an irritable bladder or suffering from gonorrhœa often finds relief by copious linseed drinks.

OL UM A ACHIS

Arachis Oil. (Ol. Arach.)

Syn.—Nut Oil, Ground-nut Oil, Pea-nut Oil.

Syn. IV.—*China-badamier tel* Beng. *Mungphali tel*, Hind

Source.—Expressed from the seeds of *Arachis hypogæa*

Characters.—Pale-yellow liquid, odour, faint, and nut-like, taste, bland, nutty Sp gr 0.916 to 0.920. Becomes rancid and thick slowly.

Composition.—*Olein*, also contains the glycerides of *hypogæic*, *arachidic* and *linoleic acids*

B.P. Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls

PHARMACOLOGY AND THERAPEUTICS

Externally—The oil makes a good substitute for olive and almond oils, and has long been used in Indian pharmacy in their stead.

Internally.—It has a gentle aperient action. The seeds are very nutritive as they contain 31.0 p.c. of nitrogenous compounds, 37.8 p.c. of starch and sugar, and 11.8 p.c. of fatty matter. They are largely eaten in India and Africa.

GLYC RINU

(Glycer.)

Glycerin. $C_3H_5O_3$

Source.—Obtained by the hydrolysis of fats and fixed oils.

Characters.—A clear, colourless, inodorous, sweet, syrupy liquid, miscible with water and alcohol (90 p.c.), insoluble in ether, chloroform, and fixed oils. It is neutral, hygroscopic, sp. gr 1.260 to 1.265

B.P. Dose.—60 to 120 ms. or 4 to 8 mls, by rectal injection:—30 to 120 ms. or 2 to 8 mls

Enters into.—The preparation of all Glycerins, and Cataplasma kaolini.

OFFICIAL PREPARATION

1 Suppositorium Glycerini.—70 p.c

PHARMACOLOGY

Externally.—Glycerin adheres to the surface to which it is applied and absorbs moisture. It keeps the part moist

and does not itself evaporate. It readily penetrates the unbroken skin, and carries with it many substances, such as alkaloids, when mixed with it. It is an antiseptic, emollient and demulcent. It renders the skin supple, especially when diluted with water, allays burning or tingling. Owing to its avidity for water, undiluted glycerin is irritant to the mucous surface and to the skin. If introduced into the cervical canal, it provokes uterine contraction.

Internally. Alimentary canal.—Undiluted glycerin makes the mouth clammy and sticky. It is easily absorbed and oxidised in the body. In large doses it acts as a laxative. Injected into the rectum, it moves the bowels by inducing peristalsis from its local irritant effects caused by the absorption of moisture from the mucous surfaces.

Blood.—It is freely absorbed by all surfaces. Subcutaneous injections cause destruction of red corpuscles, and the hæmoglobin is dissolved in the plasma, leading to hæmoglobinuria.

Elimination.—Glycerin is excreted from the body as propionic, formic and other acids. The urine of persons taking glycerin gives the copper and fermentation tests for sugar due to the appearance of reducing product which is not sugar.

PHARMACEUTICAL USES AND THERAPEUTICS

Pharmaceutically.—On account of its valuable physical properties, glycerin is peculiarly fitted for pharmaceutical and dispensing uses. It makes an excellent all-round excipient for pills. It is used in the preparation of suppositories, pessaries, pastils, jellies, glyco-gelatin preparations and ointments; and as a solvent for many alkaloids, active principles, acids, alkalies, neutral salts, glucosides, iodine etc. It is a valuable adjunct to lotions for the skin and the hair. As a flavouring agent it is largely employed as a substitute for syrups in mixtures. As a sweetener and preserver of mixtures it is admirably suited to the Indian climate.

Externally.—As an *emollient*, glycerin diluted with water (1 in 3), or glycerinum c. aqua rosæ (glycerin 2, rose water 3), is the best application for chapped lips and hands, rough, dry, furfuraceous skin and for every kind of skin disease, such as herpes, eczema, etc., which require an emollient. Mixed with boric acid it is serviceable in pityriasis of the body and scalp. It removes dryness of the meatus of the ear, and heals excoriation and fissures. It is the best preventive for bed-sores when gently rubbed into the parts before they become tender and red. A 5 p.c. solution of both glycerin and Friar's Balsam in rose water prevents a further breaking out of acne when once it is checked. Cotton-wool soaked in glycerin and applied to the os uteri, by causing a

copious watery discharge, relieves congestion of that organ. For its hygroscopic property it forms a valuable ingredient of cataplasma kaolini.

Internally. **Alimentary canal.**—The lips, the tongue and the gums covered with sordes, as in acute febrile diseases, are easily cleaned by keeping them moist with glycerin. As a laxative it is not used by the mouth, but it may be combined with castor oil to render the latter less disagreeable and more effective. Glycerin (60 to 240 ms.) may be injected into the rectum by a special syringe to open the bowels in constipation. The official suppository may conveniently be used for the same purpose and is particularly useful in cases where there is a prejudice against the use of enemata. The injection of glycerin is contra-indicated in piles and is useless if the faecal accumulation is very high up.

Lungs.—A tea-spoonful of glycerin alone or diluted with water often relieves cough. A little lemon juice added to it makes it more efficacious and moderates its sweetness.

EL PU ATU

Purified Honey. (Mel. Depur.)

Source.—Commercial honey melted, allowing the scum to rise to the surface, and strained, the specific gravity being adjusted to 1.36 by the addition of water

Characters—A thick, syrupy, translucent, pale-yellow or yellowish-brown, liquid. Odour, honey-like. Taste, sweet

Composition—A mixture of several kinds of sugar, *vis* cane-sugar, grape-sugar, lævulose, also wax, pollen, colouring and odorous matters, etc.

Enters into—Mel Boracis, Oxytel Scillæ

OFFICIAL PREPARATION

1 Oxytel—B.P. Dose—30 to 120 ms or 2 to 8 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Honey is a demulcent and is used as a covering to boils and excoriations.

Internally.—It increases the secretions of the mouth and throat, and acts as a demulcent, relieving dryness of the mouth, cough, difficulty in swallowing. Hence it is used in gargles, cough mixtures and linctuses. It is a nutrient, and in large doses a laxative, and is therefore used to open the bowels of infants. Honey makes an excellent vehicle for castor oil and for administration to new-born babes and infants.

GLYCY HIZA

Liquorice. (Glycyrrh.)

Syn.—Glycyrrhizæ Radix

Syn IV—*Jashthmadhu*, Beng. *Jethi-madh*, *Mithi-lakdi*, Hind.

Source.—The peeled root and peeled subterranean stem of *Glycyrrhiza glabra*, and other species

Characters.—Long, cylindrical, before being peeled dark brown, and

longitudinally wrinkled; when peeled, yellow, fibrous. Fracture, brown. Odour, faint. Taste, characteristic, sweet, free from bitterness.

Composition.—(1) *Glycyrrhizm*, a sweet, white, crystalline powder consisting of calcium and potassium salts of glycyrrhizic acid. Also contains *asparagin*, grape sugar, resin, starch, malic acid, etc.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

OFFICIAL PREPARATIONS

1. *Extractum Glycyrrhizæ*.—B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.
2. *Extractum Glycyrrhizæ Liquidum*. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
3. *Pulvis Glycyrrhizæ Compositus*. *Syn. Pulvis Pectoralis*.—Liquorice and senna leaf each 16 p.c. B.P. Dose.—60 to 120 grs. or 4 to 8 grms.

NON-OFFICIAL PREPARATION

1. *Mistura Opii et Glycyrrhizæ Co.*, U.S.P. *Syn. Brown Mixture*.—Fluid extract of liquorice 120 c.c., potassium antimony tartrate 0.24 gm.; camphorated tinct. of opii 120 c.c.; spirit of nitrous ether 30 c.c.; glycerin 120 c.c.; water q.s. to 1000 c.c. Dose, U.S.P.—1 dr. or 4 c.c.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Being sweet it increases the flow of saliva. It is an excellent **demulcent**, and is largely employed in relieving sore-throat, for which purpose pieces of "stick liquorice" are kept in the mouth. The dried root has no laxative effect, but pulv. glycyrrhizæ co. is a mild laxative owing to senna and sulphur. Liquorice makes an excellent excipient, and disguises the taste of many nauseous drugs.

ACACIA

Acacia. (Acac.)

Syn.—*Acacie Gummi*.

Syn. I.V. *Gaud*, Beng. *Babul ka-gand*, Hind.

Source.—A gummy exudation from the stem and branches of *Acacia senegal*, and other species of *Acacia*.

Characters.—Ovoid or round tears or masses; colourless, glistening, or yellowish angular fragments; odourless; taste, bland; mucilaginous.

Solubility. Entirely in water, insoluble in alcohol.

Composition.—*Arabin* or *arabic acid*, combined with calcium, potassium, and magnesium. Also contains oxidising, peroxidising, and diastase ferments.

OFFICIAL PREPARATIONS

1. *Injectio Sodii Chloridi et Acaciæ*.—Contains 6 p.c. *acacia*.
2. *Mucilago Acaciæ*. *Syn. Mucilage of Gum Acacia*.—40 p.c. B.P. Dose.—60 to 240 ms. or 4 to 16 mils.
3. *Pulvis Tragacanthæ Compositus*.—*Acacia* 20 p.c. B.P. Dose.—10 to 60 grs. or 0.6 to 4 grm.

NON-OFFICIAL PREPARATION

1. *Syrupus Acaciæ*, B.P.C.—Mucilage of *acacia* 25, Syrup to 100. Dose.—1 to 4 drs. or 4 to 16 mils.

PHARMACOLOGY AND THERAPEUTICS

Gum *acacia* is a demulcent and is given in sore-throat, catarrhal states of the gastric, intestinal or bronchial mucous membranes and in irritant poisoning. In pharmacy, it is chiefly used to suspend insoluble powders, and to emulsify resins and oils, and as an excipient for pills, jujubes, etc. The injection has been used intravenously in shock following hæmorrhage (see page 85).

TRAGACANTHA

Tragacanth. (Trag.)

Syn.—Syrian Tragacanth.**Source**—A gummy exudation obtained by incision from *Astragalus gummifer*, and other species of *Astragalus*.**Characters**—Thin flattened flakes, irregularly oblong, or more or less curved, marked on the surface by concentric ridges 2.5 cm. long, and 12 mm. wide, white, or pale yellowish-white, somewhat translucent. Very tough and must be heated to 49°C before it can be powdered. Without smell or taste. **Solubility**.—Sparsely in cold water which converts it into a gelatinous mass, coloured violet by iodine.**Composition**—The part soluble in water consists of *Polyarabinan trigalactan-geddlic acid*, which on hydrolysis yields *arabinose*, *galactose*, and *geddlic acid*. The insoluble portion yields *α*- and *β*-*tragacanthanxylan bassoric acids*, which yield on hydrolysis *tragacanthose*, *xylose* and *bassoric acid*. A little starch.

OFFICIAL PREPARATIONS

1. **Mucilago Tragacanthæ**.—Tragacanth 125 p.c. B.P. Dose.—60 to 240 ms. or 4 to 16 mils
2. **Pulvis Tragacanthæ Compositus**.—Tragacanth 15 p.c. B.P. Dose.—10 to 60 grs or 0.6 to 4 grm

NON-OFFICIAL PREPARATIONS

1. **Linimentum Exsiccans** *Syn*—*Bassorin Paste*.—Tragacanth 5, Glycerin 2, Alcohol (90 p.c.) 10, Water to 100. Dries quickly on the skin producing a pleasant cooling sensation. May be medicated with any drug
2. **Gelanthum** (Unna).—Tragacanth 2½ dr. in water 10 oz. for 4 hours in a steam bath, press through muslin, add glycerin 6 dr. Heat on a water bath for 1 hour, add thymol water q.s. to 12 oz.

PHARMACOLOGY AND THERAPEUTICS

In the form of Unna's Gelanthum, or the various "Bassorins" tragacanth is very useful in the treatment of many skin diseases. It is a demulcent, and when mixed with glycerin forms a soothing application in sore-throat but its chief use is to aid the suspension of heavy insoluble powders in mixtures. As a rule the mucilage is to be preferred to the compound powder which, on account of the starch it contains, is apt to ferment.

✓ **A YLU**
Starch

Syn IV.—*Shetsar*, Beng.**Source**—Polysaccharide granules, obtained from the grains of maize, *Zea Mays*, or of rice, *Oryza Sativa*.**Characters**.—In fine, white powder or in irregular, angular masses; odourless. Readily reduced to powder.**Incompatible**.—Iodine.

OFFICIAL PREPARATION

Glycerinum Amyli—85 p.c

PHARMACOLOGY AND THERAPEUTICS

Externally.—Starch is bland and non-irritating and may be used as a protective and absorbent in weeping eczema or excoriated and inflamed surfaces, as light burns. In the

form of violet powder, which is merely perfumed starch, it is used to prevent excoriation of the skin of infants. Generally it is used as a basis for dusting powders and insufflations. Glycer. amyl. is a good application for chilblains and chapped hands.

Internally.—It is a food and an antidote for poisoning by iodine. Mucilage of starch (1 in 40) forms a basis for enemas and to suspend insoluble powders and oils. In the form of barley water starch is largely used as a demulcent and for diluting milk for infants.

SAPO ANIMALIS

(Curd Soap. (Sap. Animal.)

Syn.—Sodium Stearate.

Source.—Made from sodium hydroxide and purified solid animal fats, consisting principally of stearin.

Characters.—Yellowish-white or greyish-white, substance; nearly odourless; horny and pulverisable when dry, easily moulded when heated. *Soluble* in alcohol (90 p.c.), sparingly in cold, but soluble in hot water.

✓ SAPO DURUS

(Hard Soap. (Sap. Dur.)

Syn.—Castile Soap; Olive Oil Soap, Sodium Oleate.

Source.—Soap made from sodium hydroxide and olive oil.

Characters. A greyish white, yellowish-white, or greenish-white substance; nearly odourless. Becomes horny and pulverisable when dry. *Soluble* in 20 parts of cold water, in 15 parts of hot water, almost completely soluble in alcohol (90 p.c.).

✓ SAPO MOLLIS

(Soft Soap. (Sap. Moll.)

Syn.—Green Soap; Potassium Oleate.

Source.—Soap made with potassium hydroxide and olive oil.

Characters.—Yellowish-white to green, almost inodorous, unctuous substance. *Solubility.*—In alcohol (90 p.c.), and in water.

OFFICIAL PREPARATION

1. *Linimentum Saponis.* *Syn.*—*Opodeldoc.*—Soap 8 p.c.

NON-OFFICIAL PREPARATION

1. *Liquor Saponis Æthereus, B.P.C.* *Syn.*—*Æther Soap.*—Oleic Acid 35, Caustic Potash, *q.s.*, Water *q.s.*, Oil of Lavender 0.2, Alcohol (90 p.c.) 15, Ether to 100. For surgical use prior to operations.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Soap is a valuable cleansing agent due to partial hydrolysis and formation of free alkali when it comes in contact with a large quantity of water. This alkali saponifies and dissolves the fat of the skin and softens the epidermis. It is therefore largely used in various skin diseases to remove the epidermis and to make the deeper layers accessible to other remedial measures. Owing to its power

of penetration, it is used as a vehicle for drugs intended to be absorbed or to act through the skin. Seborrhœa, scaly eczema, sycosis and ichthyosis do well when the parts are washed with soft soap before any remedial agents are applied. The liniment rubbed over sprained or stiff joints promote the absorption of inflammatory products, but how far this effect is due to the friction or to the drug, is difficult to say. Soaps can be medicated with various drugs. Mollin or superfatted soap is not an irritant and may be used in many skin diseases, and makes a good basis for ointments.

Internally.—Hard soap is antacid, and not being easily soluble may be used to neutralise acid in any part of the intestinal tract, which the soluble alkalies cannot reach. It aids the emulsification of foods in the duodenum, and restores some of the normal constituents of bile. It is itself a gentle laxative, and corrects and aids the action of certain purgatives, such as jalap and aloes. Introduced into the rectum in the form of a cone as a suppository, it purges by reflexly contracting the rectum and colon, and is very useful in infantile constipation. Soap and warm water make an effective enema for constipation of adults.

Hard soap is used in pharmacy as a corrigens and as a basis for pills and plasters, and the soft soap as a basis for some liniments.

PA AFFINU DURU

Hard Paraffin. (Paraff. Dur.)

Source—A mixture of solid hydrocarbons, obtained from petroleum, and from shale oil.

Characters.—A colourless or white, translucent mass; odourless even when freshly cut, tasteless, slightly greasy to touch. Burns with a luminous flame. *Insoluble* in water and in cold alcohol (90 p c.), soluble in ether and chloroform.

OFFICIAL PREPARATIONS

1. Unguentum Paraffini.—Hard paraffin 8 p c.
2. Unguentum Simplex.—Hard paraffin 10 p c.

USES

In pharmacy it is used as a basis for ointments, specially for use with drugs not intended to be absorbed. It is also used as an excipient for silver nitrate and permanganate of potash pills.

PA AFFINU LI UIDU

Liquid Paraffin (Paraff. Liq.)

Syn.—Liquid Petrolatum, USP; Adepsin Oil; Glymol; Oleum Deelinæ; Paroleine; Chrismaline.

Source—A mixture of liquid hydrocarbons, obtained from petroleum.

Characters—Transparent, colourless, tasteless, odourless, oily liquid. Sp. gr. 0.880 to 0.895

B.P. Dose— $\frac{1}{4}$ to 1 oz. or 7.5 to 30 mls

PARAFFINUM OLLE ALBUM

(Paraff. Moll. Alb.)

White Soft Paraffin

Syn.—Petroleum Jelly.**Source.**—A mixture of semi-solid hydrocarbons, obtained from petroleum, and bleached.**Characters.**—A white, translucent, soft mass; unctuous to touch. Odourless and tasteless.**OFFICIAL PREPARATION**

1. Unguentum Aquosum.—Aqua 24 p.c.

PARAFFINUM MOLLE FLAVU

(Paraff. Moll. Flav.)

Yellow Soft Paraffin

Source.—A mixture of semi-solid hydrocarbons, obtained from petroleum.**Characters.**—A pale yellow to yellow, translucent, soft mass. Unctuous to the touch. Almost free from odour or taste. Insoluble in water, in alcohol (90 p.c.), soluble in ether and chloroform.**PHARMACOLOGY AND THERAPEUTICS**

Externally.—Paraffins neither irritate the skin, nor become rancid, nor are they acted upon by acids, alkalies or oxidising agents. They are therefore superior to lard, and form a valuable basis for ointments meant for local action only. As they are very feebly absorbed, they cannot be used as a basis where constitutional action of drugs is intended. Liquid paraffin is a useful solvent for many drugs intended for hypodermic injection. Hard paraffin is used to give consistence to softer ointments, especially in India during the hot weather. As they are non-irritant and do not undergo a change by exposure to the air, they are very useful lubricating and protecting agents in psoriasis, xeroderma, chapped hands and nipples, eczema, sunburn, etc. Paraffin forms an excellent dressing for burns. A thin film of liquid or melted paraffin is painted on the clean burn and then covered by a thin layer of cotton-wool which is covered by a second layer of paraffin. The dressing is renewed daily and is easily removed. It is largely used in the form of Ambrine which contains 5 p.c. oil of amber.

Internally.—Cocaine, menthol, ephedrine, etc., are dissolved in liquid paraffin for application as a spray to the throat in laryngeal affections. Liquid paraffin is given with the hypophosphites in the form of an emulsion as a substitute for cod-liver oil, but beyond their forming a bland basis, very little is known of their effects in the tissues. Taken internally it is not absorbed, but softens and increases the bulk of the faeces. It is mildly laxative and is largely used as a lubricant in habitual constipation, colitis, ulcerations of the bowels, etc., in $\frac{1}{2}$ to 1 oz. doses. A disagreeable effect of giving liquid paraffin is that it is sometimes passed out involuntarily with the expulsion of the flatus.

ACIU OLEICU

(Acid. Oleic.)

Acid Oleic. $C_{17}H_{33}COOH$ **Syn.**—Hydrogen Oleate**Source.**—May be obtained by hydrolysis of fats, or of fixed oils, and separation of the liquid acids by expression**Characters.**—Colourless or yellowish, oily liquid, odour and taste, characteristic. Darkens on exposure. *Insoluble* in water, soluble in alcohol (90 p c), ether, chloroform, benzene.**B.P. Dose**—5 to 15 ms or 0.3 to 1 mil.**ACTION AND USES**

Oleic acid penetrates the skin more readily than fixed oils and fats, and is therefore used in pharmacy for compounding ointments containing metallic oxides and alkaloids. In the form of capsules (7½–15 ms) it is given by the mouth on an empty stomach every morning in hepatic colic and to prevent formation of gall-stones.

ADEPS

Lard

Syn.—Adeps Præparatus**Source.**—The purified internal fat of the hog, *Sus scrofa***Characters.**—A soft, white, unctuous fat. Odour, faint but not rancid. Entirely soluble in ether.**Composition.**—(1) *Olein*, 80 p c. (2) *Stearin* (3) *Palmitin*.**OFFICIAL PREPARATION**

1. **Adeps Benzoinatus.**—Benzoin 3 p.c.

ADEPS LANA

Wool Fat. (Adeps Lan.)

Syn.—Anhydrous Lanolin**Source.**—It is the purified anhydrous fat-like substance obtained from the wool of sheep.**Characters.**—A pale-yellow, tenacious, unctuous substance; with a characteristic, faint odour. *Insoluble in water*, sparingly soluble in cold alcohol (90 p c), freely soluble in ether and chloroform.**OFFICIAL PREPARATIONS**

1. **Adeps Lanæ Hydrosus.** *Syn.*—*Lanolin*.—Wool fat 70 p.c.
2. **Unguentum Simplex.**—Wool fat 5 p.c.

ACTION AND USES

Lard and wool fat are largely employed in pharmacy for making certain ointments. They are emollients. Adeps lanæ is non-irritant and is readily absorbed and is therefore used as a basis for the ointment of many active drugs.

SEVU

Suet. (Sev.)

Syn.—Mutton Suet, Sevum Præparatum.**Source and characters.**—The purified internal fat of the abdomen of the sheep, *Ovis aries*. Firm, white, unctuous fat. Taste, bland, nearly inodorous.**Composition.**—(1) *Olein*, 30 p.c. (2) *Palmitin*. (3) *Stearin*.

CERA FLAVA

(Cera. Flav.)

Yellow Beeswax

Syn. I.V. — *Mom*, Beng.

Source and characters.—Obtained from the honeycomb of the bee, *Apis mellifica*. A yellowish brown solid, somewhat brittle when cold, becoming plastic when warm. Odour, agreeable, honey-like. Fracture granular, not crystalline. *Solubility*—In chloroform, and in fixed and volatile oils.

Composition.—(1) *Myricin* (methyl palmitate), 80 p.c. (2) *Cerotic acid*, 15 p.c.

CERA ALBA

(Cera Alb.)

White Beeswax

Source and characters.—In yellowish white solid, translucent in thin layers; made by bleaching yellow wax. Odour, faint, characteristic.

ACTION AND USES

They are chiefly used as a basis for plasters and ointments. If the basis of the latter becomes too soft on account of the prevailing high temperature, extra white beeswax or yellow beeswax may be added to render it more suitable for use.

GROUP XXV**CERTAIN DIAGNOSTIC AGENTS**

Class A. Drugs used for X-ray diagnosis

1. For the alimentary canal: **Barium Sulphate** (*see* page 107), **Bismuth Salts** (*see* page 486.)
2. For the gall-bladder; **Iodophthalein** (*see* page 356)
3. For kidney affections; **Uroselectan** and **Abrodil** (*see* page 403)
4. For lungs and bronchioles; **Iodised Oil** (*see* page 323)

Class B: Drugs used for investigating liver or kidney functions

1. Investigation of metabolic functions of liver; **Lævulose** (*see* page 597)
2. Investigation of renal efficiency; **Urea** (*see* page 363), **Indigo carmine** (*see* page 403), **Methylene Blue** (*see* page 569), **Phenol Red** (*see* page 404)

Class C: Drug used for diagnosis of corneal ulcer; **Fluorescein** (*see* page 568)

GROUP XXVI**DRUGS WHOSE ACTIONS ARE MECHANICAL**

Pyroxylin, Collodion, Oil of Theobroma

PYROXYLINUM

Pyroxylin. (Pyroxylin.)

Source.—It is a nitrated cellulose, obtained by the action of a mixture of nitric and sulphuric acids on cotton wool (freed from fatty matter), and subsequent purification. Contains 11.5 to 12.3 p.c. of nitrogen.

Characters.—A white, matted mass of filaments, resembling cotton wool but harsher to the touch. Highly inflammable.

OFFICIAL PREPARATION

1. **Collodion Flexile.** *Syn.*—*Collodion*.—Pyroxylin 2 p.c.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Painted over the skin, collodion leaves a thin film from the evaporation of ether. This coating is impervious to air and moisture, and therefore causes a partial anæmia of the part by pressure on the local blood-vessels. As a *protective covering*, it may be applied to small, inflamed, broken or cut surfaces, chapped nipples or threatening bed-sores. It is particularly suited to scalp wounds, as by its contractile property it not only helps to draw the edges together, but does away with the necessity of a bandage. It may be employed to arrest local hæmorrhage from small cuts or wounds, as in leech-bites, and to close punctured openings as in paracentesis. If painted over the face in small-pox it lessens pitting, and when applied to the mouth of the urethra or orifice of the prepuce it prevents nocturnal incontinence of urine in children. Mixed with salicylic acid (*see* p. 432), it dissolves corns and warts, and with salicylic acid and zinc chloride or lactic acid, small lupoid and epithelial growths. With iodoform it forms a very effective pigment for glandular swellings and with iodine for ringworm, alopecia and inflamed, gouty or rheumatic joints.

Caution —No flame should be brought near the part until the evaporation is complete.

OLEU THEOBROMATIS

(Ol. Theobrom.)

Oil of Theobroma

Syn.—Cacao Butter. Cocoa Butter.

Source —A solid fat expressed from the seeds of *Theobroma Cacao*.

Characters —A yellowish-white solid fat; odour, slight, agreeable, resembling that of cocoa. Taste, bland, characteristic. Somewhat brittle, but softens at 25° C. Melts at 30° to 35°.

Composition.—Glycerides of *stearic*, *palmitic*, and *oleic acids*.

PHARMACOLOGY AND THERAPEUTICS

Because its melting point is below that of the human body, oil of theobroma is used as the basis for all suppositories which are intended to dissolve slowly when introduced into the rectum.

In this country it is better to make up the suppositories as directed in the Pharmacopœia, keep them in water till required, and put them on ice to harden before they are introduced into the rectum.

GROUP XXVII COLOURING AND SWEETENING AGENTS

Class A : Colouring agent
Coccus

COCCUS

(Cochineal. (Cocc.))

Syn.—*Coccus Cacti*. **Syn. IV.**—*Grimidana*, *Gringdana*, Beng., Hind

Source. The dried female insect, *Dactylopius coccus*, containing eggs and larvæ

Characters.—About 3.5 to 5.5 mm. long; oval, flat, or concave beneath convex above, transversely wrinkled, purplish-black or purplish-grey; easily powdered. Powder, dark red or puce-coloured.

Composition.—(1) *Carminic Acid*, 10 p.c. (2) *Fat*, 10 p.c. and wax, 2 p.c. *Carmine* is precipitated from the decoction by sulphuric acid and other reagents.

Enters into Tinct. Cardamomi Co., Tinct. Cinchona Co.

OFFICIAL PREPARATION

1. *Tinctura Cocci* 1 in 10. **B.P. Dose.**—5 to 15 ms. or 0.3 to 1 mil.

Uses.—Cochineal is used as a colouring agent. Alkalies turn carmine purple.

Class B : Sweetening agents

Soluble Saccharin, **Sucrose** (*see* page 594), **Dextrose** (*see* page 595), **Glucose** (*see* page 595), **Lactose** (*see* page 594), **Levulose** (*see* page 597), **Honey** (*see* page 654), **Malt Extract** (*see* page 334), **Glycerin** (*see* page 652)

SACCHARINUM SOLUBILE

(Saccharin. Solub.)

Soluble Saccharin

Syn.—*Glusidum Solubile*.

Source. A sodium derivative of *o*-benzoic-sulphinide, and is prepared by neutralising *o*-benzoic sulphinide with sodium hydroxide, or with sodium bicarbonate.

Characters.—A white crystalline powder, odourless, or faint, aromatic odour; intensely sweet. *Soluble* in 1.5 parts of water, in 50 parts of alcohol (95 p.c.).

B. P. Dose.— $\frac{1}{4}$ to 2 grs. or 0.03 to 0.12 grm.

PHARMACOLOGY AND THERAPEUTICS

In large doses, gluside is an antiseptic and passes out with the urine unaltered. It is chiefly used for its sweetening property to cover the taste of unpleasant drugs, and as a substitute for sugar in diabetes, obesity, dyspepsia, etc. Being more palatable, soluble gluside is better suited for flavouring purposes, as ordinary saccharin leaves a disagreeable after-taste.

PART IV

VACCINE AND SERUM THERAPEUTICS

The method by which resistance is conferred upon an animal towards a given disease forms the basis of the study of immune therapy. By *immunity* is meant non-susceptibility to a given disease or a given organism either under natural conditions or under conditions experimentally produced. By *tolerance* is meant partial or limited form of immunity. Although the term is generally applied to a condition produced after repeated use of certain drugs like opium, it is now used increasingly to denote the peculiar form of partial immunity that is developed in protozoal diseases like malaria. As a result of continued infection and reinfection with the malaria parasite a condition is established in which the host is able to live a more or less healthy life and to offer some resistance to reinfection while still harbouring the parasite in small numbers. This type of infection immunity is spoken of as '*tolerance*' or '*premunition*'.

Immunity for descriptive purposes may be classified as follows :—

A. Natural Immunity.—This form of immunity is possessed by man and animal either from birth or acquired during growth by virtue of its species, racial or individual peculiarities. As an instance of *species immunity* may be mentioned the immunity of hens against tetanus, and of dogs, rats and mice against tuberculosis. The immunity of certain races to certain diseases, as for example, the immunity of the negro to yellow fever is considered by some as *racial immunity*. Again some families are more resistant to certain diseases than others. Certain individuals also show varying degrees of immunity to some of the infectious diseases. In times of epidemics all persons exposed to infection do not contract the disease and even among those who develop it there are some who suffer more severely than others. Natural immunity is neither absolute nor permanent. Through the administration of large doses of infective material it is possible to break down this immunity. The immunity of the hen to tetanus for example may be overcome by giving massive doses of tetanus toxin. In the same way it is also possible to enhance natural immunity by artificial means.

Acquired Immunity.—Immunity may be acquired in two ways—*actively*, or *passively*. It is called (i) *active* when the individual's own tissues play an active part in the process of acquiring the resistance, and (ii) *passive* when the resistance is acquired through introduction from without,

of ready-made protective substances or antibodies from other animals of the same or another species.

✓ I. **Active Acquired Immunity.**—This again may arise (a) *naturally*, or (b) may be *artificially* induced.

(a) *Natural Active Acquired Immunity.*—It is well-known that an attack of an infectious disease confers upon a person a certain amount of immunity from a second attack. The immunity that is so developed is known as *natural active acquired immunity*. While in small-pox, measles, chicken-pox, plague and typhoid fever a high degree of immunity follows an attack of the disease; in influenza, pneumonia and gonorrhoea little or no immunity is conferred by an attack.

(b) *Artificial Active Acquired Immunity.*—When active immunity results from inoculation of material containing antigenic substances derived from bacteria or viruses, it is known as *artificial active immunity*. The term *vaccination* is applied to all methods of artificial active immunisation, and the material used for vaccination is known as *vaccine*. A vaccine may consist of (i) living virulent virus, (ii) living attenuated virus, (iii) dead virus, (iv) split products from viruses, or (v) toxins. Various terms are also used to denote the method of manufacture of vaccines. Thus we have *live vaccine*, in which the organism is alive and not dead; *sensitised vaccine*; *autogenous vaccine*; *stock vaccine*; *polyvalent vaccine*, which is made from several strains of the same organism isolated from different cases; *mixed vaccine*, which is made from two or more different organisms; *detoxicated vaccine*; or *lipid vaccine*, which is made by suspending organisms in oil instead of saline; *phylacogen*, which is made from solutions of bacterial cell bodies so as to be readily assimilable. Vaccines are generally given by injection in one or more doses at suitable intervals. Immunity is developed some days or weeks after the last injection, and is highly specific being effective only against the organisms used for the preparation of the vaccine. The degree and duration of immunity vary considerably in different cases. After small-pox and diphtheria vaccination, it is high and lasts a considerable time (several years); after vaccination for scarlet fever, typhoid, cholera and plague it is moderate and lasts for several months; and after vaccination for influenza, and pneumonia it is slight and lasts a very short time only. Natural active immunity confers better and more lasting protection to an individual than artificial active immunity. The latter is of very great value in the prevention of disease and of limited value in treatment.

✓ II. **Passive Acquired Immunity.**—If an animal is immunised by giving a series of injections of a vaccine in gradually increasing doses and at suitable intervals, its serum is found to contain protective substances or antibodies

which injected into a susceptible animal confers immunity upon it, provided the serum is given either at the time of, or a short time after, the occurrence of infection. The immunity that is thus conferred through the injection of serum containing specific antibodies from another animal is known as *passive immunity*. This immunity is of short duration and is of particular value in treatment—chiefly for tiding over a crisis when antibodies are lacking in the blood of the patient. In diseases like diphtheria, tetanus, measles and poliomyelitis, passive immunisation has not only been used for curative purposes but also in prophylaxis.

Anti-sera are of three different types. When bacterial cell body itself is used in the manufacture of an anti-serum the antibodies elaborated are found to have the power to agglutinate, opsonise, kill, or lyse the bacterial cell. The anti-serum in this case is known as *antibacterial serum*. On the other hand if the filtered toxin of a bacterium is used for the manufacture of anti-serum then the protective substances present in it have the power to neutralise the toxins of the organisms only and in this case the serum is known as *antitoxic serum*. In virus diseases like measles and poliomyelitis the serum of recovered cases contain specific antibodies for the virus. Such sera have been used for passive immunisation, and are known as *convalescent sera*.

✓ **Local Immunity**—This term has recently been employed by Besredka to denote the resistance offered by tissue cells to infecting agents. In opposition to the popular view he believes that the cells of the tissue attacked are the cells primarily concerned in protection and not antibodies or phagocytes. In typhoid and dysentery the causative organisms attack the intestines and in anthrax the skin. If in these diseases the tissues attacked are rendered previously insusceptible then Besredka believes that the animal would behave as if completely immune. This immunity which is dependent upon the development of nonsusceptibility of tissues to the toxic action of organisms is known as *local immunity*. In connection with *local immunity* the term *antivirus* is often used. It is the name given to the material used for inducing local immunity. It is either a killed culture of the organism or a filtrate from such culture. Experimentally Besredka has shown that the application of staphylococcus or streptococcus *antivirus* to the shaved skin of rabbits confers subsequent immunity to infection with these organisms. Some therefore believe that *antivirus* has valuable curative and protective properties. Dressings soaked in *antivirus* have been used in the treatment of staphylococcal and streptococcal infections.

Antigens—When any foreign protein substance is injected into an animal either subcutaneously or intravenously, the tissue cells react against these poisons and produce

specific antibodies. These foreign protein substances are collectively known as *antigens*. Antigens that concern us are the toxic protein substances of pathogenic bacteria and are more usually called toxins.

Bacterial toxins may be (*a*) *exotoxins*, *i.e.* poisons that are given off by the bacteria into the liquid culture media; they are entirely separate from the bodies of the bacteria and can be obtained in the broth after filtration; (*b*) *endotoxins*, *i.e.* poisons that are intracellular and incorporated with the other proteins in the body of the bacteria.

The diffusibility of the exotoxin into the culture media has an important bearing on the production of specific sera. The soluble exotoxin can be separated, injected into animals, and after a time the serum of the animals contains a definite specific body - "The Antitoxin." To this group belong the antitoxins of diphtheria, tetanus, botulinus, etc.

In the case of bacteria that only produce endotoxins, the whole organism must be injected into an animal in order to immunise it. The bacteria are broken down by the tissues, and the endotoxin is liberated, a much weaker antiserum is produced, which has a lytic action on the particular bacteria used—this serum is known as a "Antibacterial Serum." To this group belong the bactericidal sera against the streptococci, *B. coli*, anthrax, etc.

A third group of organisms form a certain amount of soluble exotoxin as well as possessing powerful endotoxins, so that animals injected with unfiltered broth cultures produce serum which is partly antitoxic and partly bactericidal, *e.g.* dysenteric and meningococcal anti-sera.

Specific antibodies.—When soluble proteins are injected into animals, a definite anti-serum is formed; the antisubstance is found to be mainly in the globulin fraction of the serum. These globulins are capable of neutralising the poisonous soluble proteins and rendering them harmless to the animal. The neutralisation may be effected as follows:

(*a*) *Antitoxin Serum.*—By the globulin fraction of the anti-serum combining with the toxin and increasing the size of the molecule without any marked alteration in the electrolytic charge of the two phases of solvent and solute. The union is a loose one and the toxin can be separated from the antitoxin by dialysis.

(*b*) *Precipitin Serum.*—By denaturalising the foreign albumins from an emulsoid into a suspensoid state, and at the same time causing an alteration in the electrolytic charge of the solution. This causes coagulation which in most cases is irreversible.

When insoluble substances, *e.g.* bacterial suspensions, red blood-cells, etc., are injected into an animal, the tissues respond differently as they have to break down masses of foreign proteins instead of dealing with proteins in solution

(exotoxins, etc.). Such masses must be broken down by the enzyme action of the fixed connective tissue cells and leucocytes into soluble products as the result of their digestive action. The different stages of this digestive enzyme are shown in the serum in the following ways :—

A. *Bactericidal Action* —This action is compared to that shown by the various enzymes in breaking down the natural proteins from an emulsoid state into metaproteins, etc., in a suspensoid state. Thus leading to :—

(1) Death of the bacteria by digestion of the natural proteins as shown by bactericidal sera.

(2) The slowing of the movement that precedes death, and the alteration of the viscosity of the plant cell as the result of digestion. The bacteria tend to clump together owing to Brownian movement and increased viscosity, as shown by agglutinins.

(3) Finally the bacteria are killed and completely dissolved into still lower proteins—"The Bacteriolysins."

B. Wright considers that after artificial immunisation by bacterial emulsions certain substances are formed in the blood—"opsonins"—which increase the avidity of the polymorphonuclear leucocytes, and so help in resisting the invasion of the tissues by bacteria.

An enzyme requires the presence of a coenzyme to digest proteins so does the analogous amboceptor; immune body or bacteriolysin requires the presence of a complement or alexin to digest bacteria, cells, etc. Most of the bactericidal sera may be regarded as sera containing specific enzymes for the particular bacteria. The delicate nature of most enzymes to temperature, violent shaking, etc., offers a possible explanation to the small value these bactericidal sera have in practice.

Specific diagnosis.—In the successful treatment of a case by vaccine or serum therapy it is essential to find the causative organism or organisms of the disease. The isolated organism, if it happens to be one that forms exotoxins enables us to employ antitoxic serum as early as possible, or if one that only forms endotoxins, the bacilli can then be killed and employed as a vaccine for the immunisation of the patient from whom they were cultivated. Various methods may be employed in determining the specific organism, *viz.*—

(1) The organism can be cultivated from the tissue and identified by the various bacteriological methods. This is the only sure and safe method.

(2) The detection of certain specific bodies produced in the host by the causative organism, *e.g.* (a) *the determination of antibodies*, specific agglutinins, as in the well-known Widal test; (b) *the determination of specific bacteriolysins*. The estimation of the agglutination depends on knowing the normal agglutinating power of the blood, that of persons

inoculated, and the correct appreciation of the existence of coagglutinins in closely allied infections, *e.g.* the typhoid coagglutinins in paratyphoid fever.

(3) Certain non-specific tests, (i) the determination of complement deviating bodies, as in the Wasserman's reaction, the cobra venom and platinum chloride tests for syphilis; (ii) in certain diseases a very definite blood picture is given by estimating the number and variety of the leucocytes present in the circulating blood.

The above mentioned tests are given in order to insist that the recognition of the specific organism is the only sure test, and the employment of it is an essential preliminary before the employment of serum or vaccine therapy.

A diagnosis having been made as to the causative organism, the next step is to apply the treatment necessary for the case. A just appreciation between the value of a given drug or vaccine must be made, in every case, thus in impetigo contagiosa the specificity of unguentum hydrargyri ammoniati renders vaccine treatment unnecessary, whilst the employment of calx sulphurata is not justifiable in folliculitis due to staphylococcus without using vaccine therapy; again in the dysentery due to Shiga's bacillus, the early use of antitoxic serum with magnesium sulphate is the only legitimate treatment to adopt.

In the treatment of bacterial diseases either with serum or vaccine, the aim is to assist the natural forces of the body in their struggle with the invading organism, either by supplying substances which will neutralise the poisons of the invader (antitoxin), or by stimulating the cells of the body, not engaged in the struggle, to manufacture antibodies. This method of treating infectious diseases is known as *specific therapy*.

Method of administration :—

(a) *Subcutaneously*.—This is the common route and is usually adopted, the best site being the loose cellular tissue of the flank or the lower abdomen, or the thigh under the fascia lata. The usual cleanliness having been done the needle is inserted by stretching the skin. When a large quantity is to be given, it may be injected on either side of the flank. The part is then covered with a little cotton wool soaked in collodion or Friar's balsam.

(b) *Intravenously*.—This route is taken in bad cases specially when the injection has been delayed. Under proper aseptic conditions there is very little risk, the serum should be diluted with three times its volume of normal saline.

(c) *Per rectum*.—This is done only when there is any objection to subcutaneous route. First wash out the rectum, and the serum diluted with normal saline to make the total bulk not less than 100 c.c. is slowly introduced into the

rectum. The utility of giving serum by this route is doubtful.

(d) *Oral* route is sometimes recommended, although it is open to doubt whether this route is of any value except when local action in the stomach is aimed at, as for instance in the treatment of gastric or duodenal ulcer. Some sera are capable of producing specific effect when given by this route, specially diphtheria antitoxin. It should be diluted to at least 50 c.c. in bulk with normal saline and given on empty stomach.

(e) *Intrathecaly*.—This route is used in the treatment of cerebrospinal fever, meningeal infections and tetanus. After making a lumbar puncture, an amount of cerebro-spinal fluid equal to the bulk of serum to be injected is first drawn out, the serum is then allowed to flow by gravity from a height of 9 to 12 inches, or injected very slowly. In either case the serum should be warmed to body temperature. It is desirable to give these injections under general anæsthesia.

The production of artificial immunity is mainly what we are concerned with in this section, and will be discussed under three heads, viz.—

- A. Bacteriophage Therapy.
- B. Serum Therapy, or passive artificial immunity.
- C. Vaccine Therapy, or active artificial immunity.

✓ A. ACTE I P AGE TH RAPHY

acteriophage.—In 1917 d'Herelle found that the filtrates obtained from the liquid fæces of bacillary dysentery cases, when added in small quantities to young cultures of *Bacillus dysenteriae* (Shiga), produced lysis of the bacteria after a period of incubation. Filtrates of these lysed cultures also showed similar lytic properties. This property was not only transmissible in series indefinitely from culture to culture but was also capable of growing in strength in each culture. From this d'Herelle suggested that the lytic agent was an ultramicroscopic virus and named it *bacteriophage*. Although the majority of subsequent workers are inclined to accept this view of d'Herelle yet there are some who believe that the lytic agent is a non-living substance of the nature of enzyme. This difference of opinion has stimulated greatly the study of phage and has led to very fruitful results. As a consequence, we are in possession of a good deal of facts regarding the properties of phage and its mode of action on bacterial organisms. Briefly, the most important properties of phage are its filtrability, its ability to multiply in the presence of young growing bacteria, its resistance to heat and alcohol, its susceptibility to acids and antiseptics, and its ability to act as an antigen. And as regards its action on organisms we know that in the presence

of specific phage bacteria may get lysed, alter in virulence, change their cultural characteristics and become modified as regards antigenic properties. The organisms most susceptible to such action by phage are the members of the colon-typhoid and dysentery group and the vibrios.

The value of phage so far as the clinician and the public health worker are concerned is dependent upon its therapeutic value. In diseases like cholera and dysentery the use of a specific highly potent phage is said to be of some value both in treatment and prevention. In India at the present time phage is being manufactured in several important laboratories on a large scale and is being tried extensively in the field for the cure and control of cholera. Experiments so far carried out independently in the provinces of Madras, Assam and United Provinces, have not yielded any conclusive results. All that can be said at present regarding the value of phage in cholera is (i) that in prophylaxis there is some evidence that administration of phage helps to reduce mortality though not morbidity, and (ii) that in treatment giving of phage is better than giving no treatment, but it is not better than giving other recognised forms of treatment.

Administration of Bacteriophage.—To be of any use it should not be given with any acid or antiseptics. It acts well in an alkaline medium, therefore alkalies can be given freely, or just before its administration. It is given in doses of 2 c.c. on an empty stomach diluted with a little water, either twice a day or oftener. No other drug, specially antiseptics, should be given at least one hour before and after its administration.

Bacteriophage has been prepared for typhoid, bacillary dysentery and cholera. The value of typhoid bacteriophage is doubtful and is used during the early stage of the disease. The dysentery phage is however useful in both acute and chronic cases, and gives good results when used early. Three to four ampoules should be taken daily.

B. SERU THERAPY

Under this head come the various methods by which we endeavour to cure a patient of a given disease by injecting him with the blood serum of an animal that has attained a high degree of active immunity either against the organism which is the cause of the particular disease, or against the toxin of the organism.

(a) Antitoxic Sera

The best examples of antitoxic sera are diphtheria and tetanus antitoxins. Before describing these in detail it is necessary to explain how an antitoxic serum is prepared. The steps in the process are :—

- (1) The preparation of a powerful toxin.
- (2) The gradual immunisation of an animal against the toxin
- (3) The estimation of the antitoxic power of the serum of the animal thus treated.

A large animal (usually a horse is used) is gradually immunised by the injection of increasing doses of this toxin. When a high degree of immunity is considered to have been attained, as the animal can now stand, larger doses of the toxin, the antitoxic power of its serum is tested by mixing varying quantities of serum with a fixed amount of toxin, and is expressed in immunity units.

ANTITOXIN DIPHTHERICUM, B.P.

(Antitox. Diphtheric.)

Diphtheria Antitoxin

Source—A serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by *Corynebacterium diphtheriae*. Prepared by separating the serum from the blood of animals, which have been immunised by graded injections of sterile filtrate from a culture of *Corynebacterium diphtheriae* on a fluid medium. May be used in the liquid form or may be dried. These are distributed in sterile glass containers sealed to exclude bacteria. The antitoxic globulins may be obtained from the serum by fractional precipitation, and the precipitate may be used either in solution, or dried.

Characters.—The serum is yellow or yellowish-brown. The antitoxic globulin solution is yellowish-brown or greenish-yellow. Both liquid forms are initially transparent, becoming opalescent in time. Almost odourless, with faint odour of the antiseptic. Solid forms are yellowish-white powder, or yellowish-brown flakes, and resemble liquid forms when dissolved in 10 parts of water.

B.P. Dose.—500 to 1000 Units (Prophylactic); or 10,000 to 20,000 Units (Therapeutic) by injection.

TOXIN DIPHTHERICUM DIAGNOSTICUM, B.P.

(Toxin. Diphtheric. Diagnost.)

Schick Test Toxin

Source—Used for the diagnosis of susceptibility to diphtheria. Obtained by preparing a sterile filtrate from a culture on nutrient broth of *Corynebacterium diphtheriae* which, after being allowed to mature is diluted before use so that 0.2 ml. contains the test dose. The sterile filtrate may be diluted with a sterile solution of sodium chloride to make it isotonic with blood. It is distributed in diluted and undiluted forms in sterile containers.

B.P. Dose.—(By intradermal injection) 3 ms. or 0.2 ml.

TOXIN DIPHTHERICUM CALFACTUM, B.P.

(Toxin. Diphtheric. Calefact.)

Schick Control

This is *Schick Test Toxin* heated at temperature not less than 70°C. for not less than five minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is issued for use.

B.P. Dose.—(By intradermal injection) 3 ms. or 0.2 ml.

TOXINUM DIPHTHERICUM DETOXICATUM, B.P.

(Toxin. Diphtheric. Detoxicat.)

Diphtheria Prophylactic

It is the sterile filtrate, or material derived from a filtrate, of a culture on nutrient broth of *Corynebacterium diphtheriae*. It occurs in the following forms:—

(a) **Diphtheria Toxin-Antitoxin Mixture**, prepared by adding diphtheria antitoxin to the filtrate.

(b) **Diphtheria Toxoid or Anatoxin**, prepared by treating the filtrate with formaldehyde.

(c) **Diphtheria Toxoid-Antitoxin Mixture**, prepared by treating the filtrate with formaldehyde, and adding a small quantity of diphtheria antitoxin.

(d) **Diphtheria Toxin-Antitoxin Floccules**, prepared by adding diphtheria antitoxin to the filtrate in the proportion necessary to produce a suitable flocculation, separating the floccules, and washing and suspending in physiological solution of sodium chloride.

(e) **Diphtheria Toxoid-Antitoxin Floccules**, prepared by treating the filtrate with formaldehyde, adding diphtheria antitoxin in the proportion necessary to produce a suitable flocculation, separating the floccules, and washing and suspending in physiological solution of sodium chloride.

(f) **Alum Precipitated Toxoid**, a suspension of white, slightly yellow or yellowish brown particles in a colourless liquid, prepared by treating the filtrate with formaldehyde, adding alum in the proportion necessary to produce a suitable precipitate, separating the precipitate, and washing and suspending it in physiological solution of sodium chloride.

Distributed in sterile containers.

B.P. Dose.—(By subcutaneous injection). The volume indicated on the label as the dose, on two or three occasions, at intervals of two to four weeks.

ACTION AND USES

Diphtheria antitoxin is used as a specific in the treatment of diphtheria. It neutralises the toxin elaborated by *C. diphtheriae* locally at the seat of the disease, but does not affect the vitality of the infecting organisms. The dose which was originally recommended was 1500 units; but the amount required as an initial dose increases with the lapse of time from onset of disease to the time of injection. If the case is not treated until the second day, give 4000 to 8,000 units; if till the third day, 8,000 to 12,000 units. In all cases when the larynx is involved, the initial dose should be at least 6000 units and similarly 8,000 units if nasal symptoms are present. The dose may be repeated in 6 to 24 hours. Each millilitre contains 400 units, and if there is any objection to using such a large quantity then a concentrated high potency serum should be selected which contains 2500 units or more per millilitre. The serum should always be administered as early as possible; indeed it is of less value unless given within the first 48 hours of the disease. For this reason in all cases of suspected diphtheria it is well to inject the antitoxin at once without waiting for a bacteriological report; even if the case be not one of diphtheria no harm can result. Another point to remember is that diphtheria is a much more fatal disease in children than in adults, and requires if anything larger doses of antitoxin. *Do not make*

the mistake, of reducing the dose of antitoxin in proportion to the age of the patient.

The proper place for injection is in the flank or between the shoulder blades.

Preventive Inoculation.—Diphtheria antitoxin has been employed to confer immunity in persons exposed to diphtheria. The usual dose is 500 units irrespective of age. This gives protection after 24 hours and lasts for about three weeks. It has the disadvantage of rendering the patient hypersensitive to subsequent injections of serum (see Anaphylaxis, page 682). But a more lasting immunity is afforded by the injection of the special diphtheria prophylactic, which, as described above, consist of six different kinds, in which the toxin has been made harmless either by combining with antitoxin or modified to toxoid. These may be used in preference to the antitoxin serum. The immunising power of the *toxin-antitoxin mixture* depends on the amount of the toxin and toxoid which has not been neutralised by the antitoxin, although it is possible that some of the bound toxin and toxoid are also set free. This was the original form of the prophylactic used, but since its use was attended with some danger it has been replaced by *anatoxin* or *toxoid*, which occasionally produces inflammatory reaction at the site of injection, therefore it has not been extensively used, but the immunising power is stronger. The *toxoid-antitoxin mixture* is free from this reaction. *Toxin-antitoxin floccules* when injected provoke antitoxin formation possibly due to slow dissociation of the floccules into their constituent parts. It causes no inflammation at the site of injection. A further improvement is the *toxoid-antitoxin floccules*, which are the best form of diphtheria prophylactic at present available and is absolutely safe for immunising children. The usual dose is 1 mil (15 ms.) given subcutaneously, followed three weeks later by a second dose of the same amount and one or two weeks later by a third dose of 1 mil. The *alum precipitated toxoid* is used in one injection of either 0.5 or 1 mil. It induces immunity more rapidly and is the best antigen when rapid production of immunity is essential. The reaction is not more severe than toxoid-antitoxin. It takes about one to six months to develop immunity, but once developed it will last for more than six years. This inoculation is not given in the presence of actual diphtheria where immediate protection is needed, but is used in schools, asylums, hospitals, orphanages, etc., to protect against possible outbreaks.

As a rule the prophylactic injections are given after testing the patient's susceptibility to infection with Schick test toxin. This is done by injecting intradermally 3 ms. (0.2 mil) of toxin on the forearm, and since the skin reaction may be due either to the specific toxin, or to non-specific substances

present, a control test is made on the opposite arm with the Schick control in order to exclude reactions due to non-specific substances. A positive reaction indicates that the individual is susceptible to diphtheria, and this is shown by the appearance within twenty-four to thirty-six hours of a circumscribed area of red flush. A negative reaction indicates that the subject is immune to diphtheria and is shown by the absence of reaction in the arm.

ANTITOXINUM TETANICUM, B.P.

Tetanus Antitoxin. (Antitox. Tetanic.)

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by *Bacillus Tetani*. Prepared by the same way as diphtheria antitoxin, except that the animal is immunised with the filtrate from a culture of *B. Tetani*.

Characters. The same as diphtheria antitoxin.

B.P. Dose.—Prophylactic, 1000 to 2000 Units; Therapeutic, 20,000 to 40,000 Units; by injection.

ACTION AND USES

The main use of antitetanic serum is for the prevention of tetanus following contused and lacerated wounds. For this purpose 1000 to 3000 units are injected as soon as possible and if the wound is extensive and badly lacerated a second injection is given within 1 to 5 days. This serum when used for prophylactic purposes should contain not less than 300 units (- 150 American units) per mil. The dried material must not contain less than 3000 units per gramme. When the serum is used for curative purposes the potency must not be less than 1600 units per mil and solid preparations of not less than 3,000 and 16,000 units per gramme. The tetanus bacillus usually grows in the wound only for the first few days after injury, and it is during this short space of time that most of the toxin is elaborated and reaches the central nervous system. Once the symptoms of tetanus have developed, it means that the toxin has reached the nerve cells in the brain and spinal cord. The antitoxin molecule is too large to dialyse through the vessel walls into cerebro-spinal fluid. The serum must therefore be introduced partly *intrathecally* and partly intravenously, the dose being 20,000 units, to be repeated on two successive days if necessary. Even larger doses (80,000 to 200,000) have been recommended *intravenously*, which prevent further toxin from the wound reaching the central nervous system. It stands to reason that subcutaneous injection of small doses is useless to cure tetanus. When combined with intravenous injection of hexamine it gives better results (*see page 398*).

ANTITOXINUM EDE ATIENS, B.P.

(Antitox. (Edemat.))

Gas-gangrene Antitoxin (œdematiens)

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by *Clostridium œdematiens*. Prepared in the same way as other serums except that the animal is immunised with the filtrate of a culture of *Clostridium œdematiens*. The serum may be used in the liquid form or may be dried

Characters.—The liquid serum is yellow or yellowish-brown. The solution of antitoxic globulins is yellowish-brown or greenish yellow. Both liquid forms are initially transparent, but become faintly opalescent on keeping. They are odourless with a faint odour of any antiseptic used. The solid forms are yellowish-white powders, or yellowish-brown flakes. When dissolved in 10 parts of water, they resemble the liquid forms in colour and appearance.

N.B. The label should state —(1) whether the product is serum, dried serum, solution of antitoxic globulins, or dried antitoxic globulins, (2) the date after which it should not be used. It should also state the minimum total number of Units in the container, either (a) the number of units in mils or gms, or (b) the total number of mils of liquid, or grammes of dried product, in the container.

B.P. Dose.—*Prophylactic*, 20,000 Units; *Therapeutic*, 50,000 to 100,000 Units, by injection

ANTITOXINU WELCHICI, B.P.

(Antitox. Welchii.)

Gas-gangrene Antitoxin (perfringens)

It is a serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by *Bacillus perfringens* (*Bacillus Welchii*).

Prepared in the same way as other serum, except that the animal is immunised with the filtrate from a culture of *Bacillus perfringens* (*B. Welchii*). Characters are the same as other sera

B.P. Dose—*Prophylactic*, 4,000 Units, by injection; *Therapeutic*, 10,000 to 20,000 Units, intravenously.

ANTITOXINU VI IOSEPTICUM, B.P.

(Antitox. Vibrioseptic.)

Gas-gangrene Antitoxin (vibrio septique)

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by the *Clostridium*, commonly known as *Vibrio Septique*

Prepared in the same way as other sera except that injections are made with the filtrate from a culture of the *Clostridium*, commonly known as *Vibrio Septique*, in a fluid medium.

B.P. Dose—*Prophylactic*, 5000 Units, *Therapeutic*, 10,000 to 20,000 Units, by injection

ACTION AND USES

Gas-gangrene is a gangrene of the body tissues caused by the different gas-producing bacteria. Gas-gangrene may occur from infection with three different types of organisms and the serum should be selected according to the invasion with the particular type. In severe forms, the tissue when pressed crepitates from the liberation of gas inside. Infection with these organisms is the cause of peritonitis and intestinal paralysis which follow abdominal operations; therefore it is used as a prophylactic in acute intestinal obstruction, appendicitis,

and in acute peritonitis with obstruction, when 4000 units are injected before operation intravenously, followed by intramuscular injections of smaller doses. Larger doses (10,000 units) are used for curative purposes intravenously, followed by smaller doses until the bowels act regularly.

ANTITOXINUM STAPHYLOCOCCICUM, B.P.

(Antitox. Staphylococc.)

Staphylococcus Antitoxin

It is a serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by certain strains of *Staphylococcus*. It is prepared in the same way as other serums except that injections are made with the sterile filtrate from a culture of *Staphylococcus pyogenes* in a suitable medium.

Characters. Same as other serums

Labelling should be same as other sera.

B.P. Dose.—5000 to 20,000 Units, by injection.

ACTION AND USES

Staphylococcic antitoxin is used in cases of generalised toxæmia or septicæmia due to staphylococcus infection, either as a prophylactic in doses of 2,000 to 4,000 units, or as a curative. The prophylactic dose is given when there is risk of general infection in cases of carbuncles, mastoiditis, osteomyelitis, or before operations. Majority of the staphylococcal infections of the skin improve under local treatment, with some a generalised toxæmia or septicæmia may follow which demand administration of staphylococcus antitoxin. It is chiefly efficacious in pyæmic cases.

Staphylococcus locoid, prepared by treating the toxin with formaldehyde, is often useful in chronic osteomyelitis, persistent boils, and other skin affections due to staphylococcus. It is given by weekly injections in doses of 0.05 to 1 mil.

SERUM ANTIDYSENTERICUM (SHIGA), B.P.

[Serum Antidysenteric. (Shiga)]

Anti-dysentery Serum (Shiga)

It is a serum, or a preparation from serum, containing the immune substances, which have a specific value, when injected into persons infected by *Bacillus dysenteriae* (Shiga).

It is prepared in the same way and has the same characters as other similar sera, except that the animals are immunised with cultures, or filtrates of cultures, of the *B. dysenteriae*.

B.P. Dose.—4,000 to 10,000 Units (by injection).

ACTION AND USES

Its early use improves the outlook of bacillary dysentery and whenever possible it should be given intravenously after first testing the sensitiveness of the patient with $\frac{1}{2}$ to 2 c.c. of the serum given subcutaneously twelve hours before the large intravenous dose. Shiga claims that by its use he has reduced the mortality from bacillary dysentery in Japan from 35 p.c. to 9 p.c. This was certainly the general ex-

perience during the war. The dose is 20 c.c. and should be given if possible within the first 24 hours of the disease; after 48 hours it has little curative value. It is important to use a polyvalent serum as there are various strains of this bacillus. Ordinarily 1 c.c. is equal to 1000 units, and the most potent preparation contains as much as 5000 units per c.c.

SE U ANTI ENING COCCICU , B.P.C.

(Serum Antimeningococcic.)

Anti-meningococcus Serum

It is a serum obtained from the blood of horses which have been immunised against strains of the meningococcus (*Diplococcus intracellularis meningitidis* Weichselbaum or *Neisseria meningitidis*), isolated from different sources. Four serological types of the meningococcus are known, viz. type I, II, III, and IV, and the serum is prepared by immunising the horses to all four types. The serum is a polyvalent serum. Group I corresponds to Gordon's types I and III, and Group II, to Gordon's types II and IV.

Dose.—10 to 30 mls by intrathecal or intravenous injection

ACTION AND USES

The serum ordinarily in use is a polyvalent one prepared against a number of strains belonging to the different types of meningococci. During an epidemic period the strains isolated usually belong to types I and III (Group I) and when the type of the organism isolated from a case can be determined, and it belongs to either of these, a Group I serum may be used. The serum should be injected both intrathecally and intravenously. In giving injections by lumbar puncture the cerebro-spinal fluid escaping under pressure should be measured and replaced by a smaller quantity of serum. The serum should be warmed to body temperature by immersion in water at 40°F. and at least 30 c.c. given if possible. The injection should be repeated according to the gravity of the case, and may be required at intervals of 12 to 24 hours. Intravenous injection of 20 c.c. to 50 c.c. should also be employed as early as possible. Both concentrated and unconcentrated sera are prepared. No accurate method of standardisation is available for anti-meningococcus serum.

Ferry's Antitoxic Serum.—This serum, prepared by the use of the filtrable toxin of the meningococcus obtained from young bouillon cultures, is at present under trial. The serum is standardised and is considered to have a high antitoxic value. As in the case of the other antimeningococcal serum the best results have been obtained by it when used at the earliest stage of the disease.

Dose.—20 to 40 mls intraspinally; 60 to 100 mls (with twice as much normal saline) intravenously.

Anti-venom Sera.—Sera which are capable of neutralising the toxic action of the venoms of poisonous snakes are prepared in different parts of the world against the venoms of local species. The Pasteur Institute, Paris, prepares four kinds for use against the venoms of snakes occurring in Europe, Africa (2) and India and Egypt.

Other anti-venom sera are prepared in India, South Africa, Australia, South America and other countries for local use.

The principle of their preparation is the same as in the case of other antitoxic sera, horses being immunised by the injection of progressive doses of solutions of the dried snake venom instead of filtered bacterial toxins. Anti-venom sera are standardised accurately by determining the amount of serum required to neutralise a given quantity of venom when a mixture of the two is injected into test animals.

Dose.—100 mls or more, intravenously.

Kasauli Antivenene—This serum is prepared against the venoms of the Indian Cobra (*Naja tripudians*) and the Daboia (*Vipera Russellii*). The preparation issued is a solution of the pseudoglobulin fraction of the serum which contains all the effective antitoxin and represents a four-fold concentration of the original serum. The antivenene is preserved by the addition of 0.35 per cent tricoresol and retains its potency for two years. Phials of 10 c.c. are issued and it is standardised to neutralise at least 2 mg. of cobra venom and 4 mg. of daboia venom per cubic centimetre.

The contents of one or two phials should be injected in the case of daboia bite and two or more in the case of cobra bite. The injections should be repeated if the symptoms do not rapidly improve. Injections should always be given intravenously when possible as the antivenene is several times more effective by this route than when given subcutaneously or intramuscularly.

SNAKE VENOMS

Snake venom is the secretion ejected or expressed from the salivary glands of different types of snakes. It contains toxic principles which are thermostable, and coagulable proteins which are thermolabile. The main active principles are: *neurotoxin* (found in excess in cobra venom), *hemorrhagin* (found in excess in viper venom), *cytolysin*, (causes intravascular clotting). Other substances are fibrin ferment, proteolytic ferments, epithelial cells, etc.

Cobra Venom. Owing to the presence of neurotoxin and on account of its depressant action on the sensory nerve endings, it has been used as an analgesic to relieve all forms of pain specially of neuralgic nature. It is used by subcutaneous or intramuscular injection, and into the growth in malignant disease. The results have not been very encouraging and the same effect may be obtained by morphine and at a less cost. It has however been used with better result in *epilepsy*, although its use must be regarded as empirical. It has been suggested that the effect may be something in the nature of protein shock.

Venene.—Is alleged to be a mixture of different snake venoms, viz. puff-adder venom, wight-adder venom, cobra venom and mamba venom. Useful in epilepsy and in all forms of mental disturbances.

Dose 5 ms. subcutaneously as an initial dose, increased at intervals of 2, 3, and 4 weeks to a maximum of 40 ms.

Viper Venom.—The venom of Russell viper has a strong coagulant action in very small dilutions. One drop of 1 in 1000 solution will clot 10 drops of hemolytic blood in 17 seconds, and a solution of 1 in 100,000 in 60 seconds. It has therefore been used as a powerful hemostatic to stop oozing of blood after operation of tonsillectomy, after extraction of tooth, in scurvy, and in hemophilia.

Stypven is Russell viper venom for local application to control bleeding. The solution is prepared fresh and remains stable for seven days.

Mocassin Venom.—Mocassin snake venom is used subcutaneously or intradermally in doses of 0.4 mil of a 1 in 3000 solution. Since it decreases the permeability of the capillaries it has been used in purpura hemorrhagica and other forms of internal hemorrhages, e.g. menorrhagia but not in hemophilia.

(b) Antibacterial Sera

In the preparation of these sera the immunisation has been carried out by the injection of living or dead bacteria which are the cause of the disease against which it is wished to secure protection. They are not antitoxic but they are bactericidal. In addition to this there is one very important difference between antitoxic and antibacterial sera. Whereas in antitoxic sera the actual substance which

neutralises the toxin is of the nature of a chemical antidote, the bactericidal effects of the antibacterial sera require the presence of two distinct substances which are called the "immune body" and the "complement." The immune body is only developed in the serum after the injection of bacteria, but once developed it is fairly stable. The complement on the other hand is present in normal serum in a small quantity but it is easily destroyed by heat, and it rapidly disappears from the serum after withdrawal from the body. The complement appears to be of the nature of a ferment and it is probable that it is the actual bactericidal agent, whilst the "immune body" is merely the connecting link between it and the bacterium upon which it acts.

Be that as it may, there can be no doubt of the following facts:—

1. In order that an antibacterial serum may be of any use the presence of both "immune body" and "complement" is necessary.

2. The "complement" rapidly disappears from the serum after it has been withdrawn from the body

3. The "complement" which exists naturally in human blood serum does not appear to act in conjunction with the "immune body" contained in the serum of the horse.

The practical result is that all these sera must be fresh, and to prevent deterioration they are kept in an ice chamber. They were largely manufactured by various chemical firms with the hope that because the diphtheria antitoxin had a distinct curative effect, that every other bacteria whether they produced an exotoxin or not, should give similar results.

SE U ANTIPN U OC CCICU I, B.P.

(Serum Antipneumococc. I)

Antipneumococcic Serum (Type I)

It is a serum, or a preparation from serum, containing the immune substances which have a specific therapeutic action, when injected into persons suffering from certain diseases due to *Diplococcus pneumoniae*.

It is prepared by separating the serum from the blood of animals, which have been immunised by graded injections of cultures of *Diplococcus pneumoniae* (type I). The serum may be used in the liquid form or may be dried. The globulins, containing the specific immune substances, may be obtained from the serum by fractional precipitation, and the precipitate may be used either in solution or dried.

Characters—Same as other sera

The label should state the minimum total number of Units in the container, or the number of Units in ml or in gm, or the total number of millilitres of liquid, or grammes of dried product, in the container; and the date after which the preparation is not intended to be used.

N.B.—It should not be used later than two years after the date of manufacture

B.P. Dose —50,000 to 150,000 Units, by *intravenous injection*.

SE U ANTIPNEU OC CCICU II, B.P.

(Serum Antipneumococc. II)

Antipneumococcus Serum (Type II)

The mode of preparation, characters, assay, storage, and dose are the same as for Antipneumococcus Serum (Type I) with the modification that suitable strains of *Diplococcus pneumoniae* (type II) are used in the preparation and assay of the serum.

ACTION AND USES

The discovery of serological types of pneumococci have demonstrated why early attempts to produce an effective

serum failed, and also showed that the problem was complicated by the fact that each type required its own specific serum. The pneumococcus produces a specific soluble antigen which accumulates in the blood in large quantities, and the object of serum treatment is to raise the concentration of the antibody to an adequate level. For this end the antigen already present must be neutralised, and it is therefore necessary to inject early and in large doses. The serum is not antitoxic but bactericidal, and aids phagocytosis.

The effects in cases of primary pneumonia are shown by a rapid fall of temperature and progressive disappearance of all signs of toxæmia. The cyanosis disappears after the first or second dose, which is very characteristic, and the viscid, blood-stained, rusty sputum changes to a loose, purulent expectoration.

The best results are obtained if the treatment is started early. The first dose is 10,000 units of type I and of type II antibody. As long as the temperature remains high, or in the presence of toxæmia, the injections are repeated every eight to twelve hours. Some recommend larger doses, *viz.* 40,000 to 50,000 units in moderately severe cases, and double the amount in severe cases in the first twenty-four hours. When the case is typed, a monovalent serum may be given. If due to type IV, do not give the injection after the third dose, as the antibody for these strains are so feeble that it will be of little use. Subsequent injections depend upon the condition of the patient. The serum is expensive, and if it is to be used economically the type of infection should be determined, which is not so easily possible for patients treated in their own homes. There may therefore be considerable delay which means the administration of larger doses.

It is best given intravenously, and repeated injections require considerable dexterity, specially in children.

Unpleasant symptoms such as rigors, anaphylactic shock, and respiratory distress may occur, but these should not prevent its administration as they are usually relieved by an injection of adrenaline. It is however inadvisable to inject the serum into subjects suffering from allergic conditions, *e.g.* asthmatics, or into elderly persons with arterio-sclerosis.*

It has also been used in primary pneumococcal meningitis and primary pneumococcal peritonitis.

Selazo's Serum for Anthrax.—This is an anti-bacterial serum prepared by immunising a horse against the *Bacillus anthracis*. The dose of the serum recommended in ordinary cases is 30 to 40 c.c. subdivided into three or four injections subcutaneously into different parts of the abdomen, and followed in 24 hours, if necessary, by further injections of from 20 to 30 c.c. In grave cases the injection should be intravenous, preferably into one of the superficial veins on the back of the hand. The dose in this case should be 10 c.c. fol-

* W.H. Wynn. *British Medical Journal*, Jan. 11. 1936.

lowed in an hour or two, where there is no improvement, by another similar dose.

In an ordinary case of malignant pustule, such as is seen in those dealing with hides, if seen at an early stage, a single injection may be sufficient to effect a complete cure with very little loss of substance.

Antistreptococcic serum.—It is a polyvalent serum used in different streptococcal infections, but the results are not very encouraging owing to the fact that the complement disappears very soon. Fresh serums, if available, can be used with some success in puerperal sepsis, erysipelas, and other streptococcal infections.

NOR AL S U

Antilytic Serum

It is generally prepared from the blood of healthy horse or sheep. The blood is first withdrawn and allowed to clot and when the serum separates it is collected and a small quantity of preservative (generally cresol) added. Finally it is tested to determine its hæmolytic and toxic properties, and bacteriologically examined for sterility.

It contains serum globulins, serum albumin, fibrin ferment and the natural chemical substances of the blood.

Dose.—150 to 300 ms. or 10 to 20 mils.

ACTION AND USES

Owing to the presence of antitrypsin, which neutralises the proteolytic ferments of pus, normal horse serum is used as a local application to promote healing of old wounds and chronic ulcers. As it contains fibrin ferment it helps coagulation of blood, and is largely used by subcutaneous or intramuscular injection as a hæmostatic in internal hæmorrhages, *e.g.* hæmophilia, which is believed to be due to deficiency of thrombokinase in the blood, purpura and in gastric and duodenal ulcers with hæmorrhage. It is given orally and subcutaneously in anæmia, and in debility due to chronic diseases.

ANAPHYLAXIS

It has been observed that if an animal is injected subcutaneously or intravenously with some foreign soluble protein, whether toxic or not, it produces no symptoms at all, but a subsequent injection of the same protein, after an interval of 10 to 15 days, produces a rapid and even fatal poisoning. This reaction is specific for each protein, *i.e.* if the first injection consisted of horse serum, any other animal serum will have little or no reaction. This phenomenon is known as "anaphylactic shock," and resembles those produced by the injection of peptone, or histamine. These poisoning symptoms are of the same type no matter what protein substance is given. The symptoms are a fall of temperature, constriction of bronchial muscles as evidenced by pulmonary distress and asphyxia, fall of blood-pressure from relaxation of the capillaries, local urticarial reactions, stimulation of the smooth muscles, *e.g.* of the stomach, intestine and uterus, and diminished coagulability of the blood. The severity of the symptoms varies in different persons and the symptoms usually pass off in the course of an hour or two.

The term anaphylaxis was originally used to explain a condition opposite to immunity, but it is now used to designate all artificially induced conditions of hypersensitiveness in man and lower animals.

This sensitiveness to second injection remains in man possibly throughout life, and is of considerable importance in serum treatment, *e.g.* a patient who had a previous course of serum and has to be treated with it again. In case there is suspicion that the sensitive state may exist, a preliminary injection of 0.1 c.c. of horse serum or the serum

to be used is given intradermally. If no reaction follows within one hour, the patient is nonsensitive.

Various theories have been advanced to explain the cause of this anaphylactic reaction. Friedberger suggested that the antigen combined with the antibody giving rise to precipitin, which by combining with the alexin circulating in the blood formed *anaphylotoxin*, the cause of anaphylactic phenomena. Others again believe that the reaction is due to disturbance of the delicately adjusted colloid balance of the blood producing deposits of fibrin. Dale and Laidlaw pointed out that an injection of histamine into guinea-pigs produced symptoms similar to those of anaphylaxis, though not identical. According to them the first injection helps the formation of a new antagonistic body *precipitin*, which penetrates the cells of unstriated muscles and other tissues, with the second injection the protein (antigen) penetrating into the cells reacts with the precipitin producing the typical symptoms.

Allergy or hypersensitiveness is the unnatural or exaggerated susceptibility to a substance which is harmless in similar amounts to the majority of the members of the same species. Allergy differs from anaphylaxis in that the reaction does not usually desensitise. Examples of allergy are the various food idiosyncrasies, e.g. appearance of urticaria, some forms of hay fever, many cases of spasmodic asthma. The nature of sensitisation may be determined in some cases by performing cutaneous inoculation with a series of protein solutions (see Protein Therapy).

After-effects of Sera.—Administration of sterile normal horse-serum even for the first time, sometimes gives rise to various clinical manifestations commonly known as *serum sickness*. The usual symptoms are cutaneous rashes, fever, oedema and joint pains. These generally appear between eight and fourteen days, and are avoided by the use of calcium. A concentrated serum is not likely to produce these symptoms as whole serum, due possibly to the smaller dose of the former. Serum sickness is also a form of anaphylactic phenomenon, although it is customary to call the severe, fatal and rare instances of death following the use of serum as anaphylaxis.

Treatment of Serum Disease.—This may be either for the prevention of anaphylactic shock or to combat the symptoms when the manifestations have, in spite of the precautions taken, appeared.

Prophylactic Treatment. 1. Calcium in the form of chloride, gluconate or lactate should be given after all therapeutic serum injections in 10 to 15 gr. doses, three or four times a day. Adrenaline (5 to 8 ms.) is always useful and may be combined with the serum, or atropine may be used.

2. The second injection may be rendered harmless by diluting it with normal saline solution in the proportion of 1 in 10.

3. **Besredka's Method of Anti-anaphylactic Vaccination.**—This consists of giving injections of small amounts of the serum before the massive injection.

Curative Treatment.—The patient should receive a purgative and kept on milk diet for a few days. If the symptoms are sudden and urgent, 4 to 6 c.c. of ether should be given intramuscularly, followed by the administration of calcium either by the mouth or as injection. Atropine hypodermically followed by adrenaline. These reactions are also controlled by oral use of pancreatin, and combined administration of sodium benzoate and salicylate.

VACCINE THERAPY

A vaccine is a sterilised suspension of organisms, living or dead, in normal saline, which when injected into a man or animal provokes formation of immunity or antibody which

directly or indirectly either destroys the infecting organisms or neutralises the toxin produced by these organisms. Vaccines may be used for the purpose of (i) *preventing disease* (prophylactic vaccines), or (ii) *curing the disease*. The vaccines are essentially the same in both cases (*i.e.* bacillary emulsions), the object being to stimulate the protective mechanism of the body to form anti-substances against the particular organisms and so resist the disease. The vaccines may be prepared from the specific organism of the disease (specific vaccines) or an organism may be used which does not cause the specific disease, *e.g.* a staphylococcus vaccine in the cure of simple parenchymatous goitre, which acts probably by stimulating the general defensive mechanism (non-specific vaccines).

Selection of the Organism for the Preparation of the Vaccines.—Vaccines are known as (a) *autogenous*, when the organism is isolated from the patient's diseased tissue, grown in pure cultures and a vaccine prepared from these pure cultures; (b) *stock*, when the causative organism is diagnosed clinically and the vaccine prepared from a stock laboratory culture. As a general rule autogenous vaccines give the best results, but usually some delay occurs in their preparation, in such cases it may be desirable to start the treatment with a stock vaccine.

Method of Injection of Vaccine.—When the dose is to be given, the neck of the glass ampoule, which has been previously well-shaken, is flamed and broken off with forceps sterilised in the flame, and the vaccine is drawn into the sterile syringe, the ampoule being held with the broken neck pointing downwards. The most convenient sites for subcutaneous injections are the upper arm near the insertion of the deltoid, or below the middle of the clavicle between it and the nipple. The skin over the spot selected for injection is disinfected with solution of iodine and the injection is given; a little iodine or collodion is finally applied to the puncture.

Control of Doses.—The dosage may be arrived at by considering the following factors.—

(a) *Toxicity of the Organism.*—The majority of the organisms we inject are highly toxic to man, *e.g.* pneumococcus, gonococcus, streptococcus, *B. pyocyaneus*, *B. coli*, Shiga, etc. and an initial dose of 5 to 10 millions is ample. With organisms of low toxicity, *e.g.* *B. typhosus*, staphylococcus, etc., an initial dose of 100 to 500 million would not cause too violent general and local symptoms.

(b) *Stage of the Disease.*—In acute stages of the disease, ample toxins are already being formed and the dose should always be small; thus in typhoid, Malta fever, dysentery, glanders, etc., the initial dose should be about 1 to 5 million, and slowly increased. The same applies to open tuberculosis,

when the T.B.E., should commence with 0 000000001. In subacute and chronic diseases much larger doses can be tolerated, e.g. 100 million.

(c) *Patient.*—*Age*, the dose can be regulated by the usual pharmacological rule of $\frac{\text{Age}}{\text{age} + 12}$. *Race*, the Indian can

usually stand larger doses of vaccines, other than tuberculin, which he is more sensitive to, than the European. *Colouration of the individual*, in practice one has noticed that light coloured individuals are more sensitive than the darker skinned.

(d) *Spacing and increasing the Dosage.*—Even when all these factors have been considered the first dose is purely an experimental one, and immunisation must be guided by watching the general, focal and local symptoms. The injections are given every three or four days until the maximum dose of 1 c.c. of 1000 million non-toxic organism, or 1 c.c. of 100 million of the more toxic ones. Three or four injections at weekly intervals are given when this dose has been reached. Usually one increases by multiples of the initial dose, viz., 0.1 c.c., 0.2 c.c., 0.4 c.c., 0.8 c.c., 1 c.c. When injecting toxic organism and dealing with sensitive patients, or in acute conditions, the increases should be made cautiously in half the arithmetical progression, viz., 0.1 c.c., 0.15 c.c., 0.2 c.c., 0.3 c.c., 0.45 c.c., 0.75 c.c., 1 c.c. Both the increases and the proper spacing of the dosage must be judged by local and focal symptoms. Actual harm can be done by giving too big doses, whilst failure to respond may be due to employing too weak a dose. In cases that are doing well, the doses can be more rapidly increased without any harmful effects.

IMMEDIATE EFFECTS OF VACCINE

These may be local, general or focal.

(1) *Local reaction*, this is likely to appear after a prophylactic dose, i.e. after a large dose. In curative treatment, when small doses are used, this reaction is as a rule not observed, unless the initial dose is large. It is doubtful if local reaction has any significance.

(2) *General reaction*, as a rule prophylactic use of vaccine is followed by this form of reaction. For instance, a rise of temperature, pains in the body or general aching, but these should subside within twelve to twenty-four hours. In the curative treatment, provided the dose is carefully regulated, general reaction that follows the prophylactic use is rarely seen. There may be a slight rise, say of one degree, and a general malaise. In fact the degree of general reaction is proportional to the amount used and the virulence of the bacterial endotoxin.

(3) *Focal reaction*.—An exacerbation of the inflammatory reaction, if present at the seat of the lesion, may take place. It should be looked upon as specific and requires careful watching. This reaction should not be aimed at, although a mild reaction is not necessarily prejudicial to the patient.

VARIETIES OF VACCINES

Vaccines used may be of the following kinds :—

(a) *Ordinary vaccine*.—It is a simple suspension of killed bacteria in normal salt solution. The bacteria are killed either by heat, or autolysis, or by some antiseptic, *e.g.* cresol.

(b) *Sensitised or sero-vaccines*.—These are made by bringing bacterial emulsion in contact with appropriate immune serum. By this process the specific antibody in the serum becomes fixed by the bacteria and this combination is termed “sensitised” vaccine.

(c) *Detoxicated vaccines*.—These are vaccines with the endotoxin removed on the idea of introducing larger doses to get proportionately larger amount of antibody. Its practical usefulness in preference to ordinary vaccine has not been established although many prefer it.

(d) *Immunogens*.—This is a more recent development and represents simple antigens almost free from toxins and from bacterial cells. In their preparation the organisms are grown on solid media, suspended in salt solution and then centrifugalised; the centrifugates forming the immunogens. Owing to their low protein content their use is not followed by any severe reactions and therefore can be given in larger doses. They may be used in acute and subacute conditions.

(e) *Formolised vaccines*.—It has been shown that when a toxin is treated with formalin it loses its toxic properties while retaining its antigenic power, *i.e.* it ceases to be a toxin, although when injected into an animal it stimulates the production of antitoxin. These are known as “toxoids” in England and as “anatoxin” in France. They are used largely for immunisation against diphtheria (*see* page 672).

(f) *Diaplyte vaccines*.—Douglas and Fleming pointed out that when bacteria were extracted with acetone they did not lose their antigenic property, while some became easily dissolved in trypsin. It was subsequently shown that a tryptic digest of the acetone extracted bacteria acted as a good antigen. Dreyer “defatted” bacteria by first washing them in formalin and then extracting them with acetone. By this process the tubercle bacilli lose their acid-fast property and the streptococci and staphylococci become gram negative, at the same time they become soluble in trypsin. Tubercle diaplyte vaccine when injected into animals produce an anti-tuberculous serum which contains more antibodies than that produced by means of bacillary

emulsion. Experience has shown that they have no special advantage over ordinary vaccines.

(g) *Antivirus*.—These are substances of microbic origin capable of local vaccination without the introduction of antibodies, and are made by growing organisms for some weeks in broth until they cease to grow. Filtrates of such cultures contain a specific inhibitory substance which has been named by Besredka as “antivirus” (see page 666).

PROPHYLACTIC VACCINES

VACCINUM VACCINIAE, B.P.

(Vaccin. Vaccinia)

Vaccine Lymph

It is a preparation of the substance obtained from the vesicles produced by inoculation of vaccinia virus on the skin of healthy animals, excluding bacterial contamination as far as possible. In viscid, colourless liquid, containing opaque white matter in suspension.

B.P. Dose — 1 minim or 0.08 mil (by scarification).

ACTION AND USES

The main object of vaccination however is to confer immunity against small-pox. The protection is less perfect and less permanent than an attack of small-pox. The susceptibility to small-pox after primary vaccination returns slowly and the immunity wears off after six years, therefore re-vaccination should be done every seven years and oftener if exposed to infection. The immunity appears after one week, generally about the eighth day of successful vaccination. The vaccine virus grows and produces an enormous number of colonies at the inoculated spot by the 8th day, when the antibodies appear which attack and digest the colonies producing toxin which cause local redness and fever. Soon however the micro-organisms are killed and the contents of the pustules become inert, but antibodies remain for a long time in the body. At this period the subject remains hypersensitive, and if re-vaccinated may develop anaphylaxis.

As a rule no complication occurs if the operation is done under strict aseptic care. But cases of *post-vaccinal encephalitis* have been recorded occurring in adults previously unvaccinated. It appears 9 to 12 days after vaccination, the onset being abrupt and accompanied by headache, vomiting and drowsiness passing on to coma. It does not occur in primary vaccination of infants or in secondary vaccination. The cause of this complication is unknown. It may be due to vaccinia virus directly, or indirectly by the activation of some unknown latent virus.

Intraspinal, intramuscular or intravenous administration of serum from individuals who have recently been successfully vaccinated has been tried by the French physicians apparently with good results.

VACCINU TYPHO-PARATYPHOSU , B.P.

(Vaccin. Typho-paratyphos.)

Anti-typhoid-paratyphoid Vaccine

Syn—T.A.B. Vaccine

It is a sterile suspension of the micro-organisms, *Bacillus typhosus*, *B. paratyphosus A*, and *B. paratyphosus B*, which have been killed. Contains 1000 million *B. typhosus*, 500 million *B. paratyphosus A*, and 500 million *B. paratyphosus B*, in 1 ml. In colourless opalescent liquid.

B.P. Dose—First dose, 0.5 ml followed after 7 to 10 days by the second dose of 1.0 ml subcutaneously.

ACTION AND USES

T.A.B. vaccine is now largely used as a prophylactic against typhoid and paratyphoid infections, and is the routine method employed in the Army and in institutions where any case of typhoid occurs. The vaccine used in India for Army purposes contains 1000 millions *B. typhosus*, 750 millions *B. paratyphosus A*, and 750 millions *B. paratyphosus B* per cubic centimetre. Two inoculations consisting of 0.5 c.c. and 1 c.c. are given at an interval of 7 to 10 days. There is generally some reaction after the first dose which consists of local tenderness and swelling with slight enlargement of the glands. A slight rise of temperature usually occurs with headache and general aching. The experience of the last war testifies to the high value of inoculation as a method of prophylaxis. In the Army in India this inoculation is repeated at intervals of 18 months. The duration of immunity is about 2 years or may be less.

The anti-typhoid vaccine (Wright) prepared from bouillon-grown cultures of *B. typhosus* only is not now used to any extent, suspensions from agar having replaced it. Vaccines consisting of *B. typhosus* without the addition of the paratyphoid strains are used in countries where the incidence of paratyphoid infections is low, e.g. U.S.A.

Anti-plague vaccine.—The vaccine manufactured in India is that of Haffkine which consists of a bouillon culture of a virulent strain of *B. pestis* grown at 80°F. for four weeks, killed by heating at 55°C. and preserved by the addition of 0.5 per cent. phenol. The dose for adult males is 3 c.c. and for women 2 c.c. Proportionately smaller doses for children are given in relation of body weight. When freshly prepared, the vaccine may give a considerable degree of reaction and it is advised that, if used within three months of the date of manufacture, the standard dose be reduced to 2 c.c. Single dose inoculation is usually employed but, when practicable, the vaccine may be given in divided doses.

Anti-plague vaccines consisting of bacterial suspensions from agar cultures are prepared at the Lister Institute, London, and the Pasteur Institute, Paris, and elsewhere.

Anti-cholera vaccine.—The prophylactic anticholera vaccine contains 8000 millions killed vibrios per c.c.; 0.5 c.c. is given as the first dose and one c.c. as the second dose a week later. The local reaction is as a rule mild, but there may be œdema, and a painful infiltration at the site of the injection. The protection lasts for about six months.

Prophylactic vaccines have been used for the prevention of colds, and pneumonia, and for dysentery in jails, asylums, etc.

Anti-rabic vaccine.—As the infecting agent in rabies cannot be cultivated on artificial media the vaccines used for anti-rabies prophylaxis are prepared from the brain and spinal cord of animals which contain the rabies virus. Pasteur found that when the virus from the dog was passed through a series of rabbits by subdural inoculation it changed its character and became 'fixed.' The 'fixed virus' is considered not to be infective for man by inoculation into the skin or subcutaneous tissues. All anti-rabic vaccines are prepared from fixed virus and several methods of preparation are employed. Pasteur's original method, which is still in use in Paris and in other Pasteur Institutes, consisted in giving a series of doses of emulsions of spinal cord of passage rabbits subjected to dessication for different periods. Live fixed virus is present in the Pasteur vaccine. The method in use in India, introduced by Semple, is the preparation of an emulsion of the brain and spinal cord of passage rabbits treated with 1 per cent. carbolic acid at 37°C for 24 hours and subsequently diluted to reduce the carbolic acid to 0.5 per cent. Semple's original treatment consisted of the daily inoculation of 5 c.c. of a 1 per cent. emulsion for 14 days. The dosage now employed is adjusted to the estimated severity of the bite, courses of treatment varying from 7 to 21 days being given and the strength of the vaccine varying from 2 per cent. to 5 per cent. passage brain. Sheep's brain is now used for bulk production of the vaccine. As the carbolised anti-rabic vaccine does not contain living virus and retains its prophylactic value for over 6 months it is not necessary for patients to be treated at a Pasteur Institute. The vaccine can be sent out to hospitals and dispensaries where treatment is easily accessible to patients. Numerous such centres have been established in India. Neuroparalytic accidents have sometimes followed the use of anti-rabic vaccine but these are very rare with the carbolised vaccine and are seldom fatal.

CURATIVE VACCINES

After the discovery of the antitoxin for diphtheria there was a rush to manufacture serums for every known bacterial disease. A few years' trial convinced the majority of medical men of the uselessness of many of these antisera, with the result that majority have disappeared in the routine treatment of disease. So it was with vaccine therapy, after the discovery by Wright of antityphoid inoculations, and the value of staphylococcus vaccines for the cure of boils, etc., a boom was started in vaccine therapy, and all and sundry were inoculated with a vaccine made from an organism that was supposed to have caused the disease. Out of this class, the following is sane view of this very useful therapeutic agent.

(a) *The Limitation of Vaccine Therapy.*—Immunity takes time to develop, 2 to 3 weeks; vaccines are therefore useless in acute diseases like pneumonia, and should be reserved for subacute and chronic affections. The blood fluids containing the antibodies must have access to the causative organism, therefore they are useless in typhoid infections of the gall bladder, and restricted in use for tuberculosis owing to the endarteritis present. The difficulty of keeping the secondary infections under control in infections of the lung, bowel, etc., and the tendency for the bacteriologist to forget the value of treatment other than vaccines.

(b) *The uses of vaccine therapy* are therefore reserved for subacute or chronic diseases; when the infective organism can readily be obtained in pure cultures; and when the antibodies produced by the graduated inoculation of these dead bacillary emulsions can come in intimate contact with the organism producing the disease; and the secondary infective flora can be limited by proper treatment.

The most important of these vaccines are :—

Wright's Staphylococcal Vaccines.—The vaccine is prepared from the organisms found in the pus. The initial dose is 100 millions increased up to 1000 to 2000 millions. The vaccine has proved most useful in furunculosis, folliculitis of the beard (sycosis), axilla and buttocks, in the secondary infections in acne. In sinuses where no dead bone, etc., is present, and to diminish the scar tissue after synovitis of the tendon sheaths.

Streptococcal Vaccines.—The initial dose is 5 millions increased gradually to 100 millions. The difficulty in preparing the vaccine lies (i) in getting the organism to grow on media, (ii) it is rarely found in pure cultures, and (iii) the identification of the pathogenic strains. Its greatest use is in eczematous conditions of the skin combined with staphylococcal vaccine. It is useful in erysipelas, otitis media and other streptococcal infections. It has a limited use in chronic rheumatoid arthritis, and sprue conditions of the gut.

B. pyocyaneus.—Dose, 10 to 100 millions, useful in ulceration of the skin, and in surgical sinuses.

B. coli.—Dose, 10 millions up to 100 millions, depending on the toxicity of the strain. The initial dose should be 5 millions or less. Of great value in *infection of the bladder and septic cystitis and pyelitis* of pregnant women. Sometimes of use in *mucous colitis*. Also useful in *perineal sepsis* when urine culture shows growth of *B. coli*.

B. dysenteriae.—*Shiga's bacillus.*—Dose, 10 to 100 millions; Flexner's, 100 to 1000 millions. Very useful in the chronic bacillary dysenteries seen in the tropics resembling a sprue. In these infections the intestinal ulcers have frequently streptococcus as a secondary infection.

D. gonococcus.—Dose, 10 to 100 millions, and should be recently made, otherwise the toxin rapidly deteriorates. The majority of cases that come for treatment are old standing cases of gleet, where a secondary infection has been superadded by urethral injections or instruments. It is not useful in acute cases, but in secondary symptoms of gonococcal infections, e.g. *arthritis, orchitis, pelvic inflammations*, etc., it gives much relief.

Pertussis Vaccine. *Syn.*—*Whooping Cough Vaccine.*—A sterile suspension of *Bacillus pertussis* (*Hæmophilus pertussis*) made from freshly isolated cultures or from cultures preserved in such a way as to retain their antigenic powers. The administration of this vaccine is indicated in the prevention and treatment of whooping cough. Inoculation of contacts confers some immunity against an attack and is therefore useful in controlling the spread of the disease. Since other organisms are found as secondary invaders, a mixed vaccine consisting of pneumococcus, B influenza, M. catarrhalis, Staphylococcus aureus, and Streptococcus hæmolyticus and non hæmolyticus is often used. Sometimes it is mixed with only B. influenza and pneumococcus.

Dose.—*Prophylactic*, 800 million, 1600 million and 3200 million organisms at intervals of three to four days. *Curative*, initial dose, 250 million, gradually increased.

Pneumococcus Vaccine.—Pneumococcus exhibits three serological groups—types I, II and III; and a heterogeneous group, comprising all those which do not conform to any of the other three types, is termed type IV.

This vaccine is used in chronic and subacute infections with pneumococcus, such as empyema, arthritis, etc. It is also useful in acute lobar pneumonia and broncho-pneumonia, and when given to susceptible individuals who were exposed to infection it will abort the attack.

Dose—25 to 50 million organisms in chronic cases, to be followed at intervals of 5 to 7 days, by further injections up to the maximum of 2000 million, the aim being to build up rapid immunity without

causing any focal reaction. In *acute lobar pneumonia*, the initial dose should not be more than 5 million, this may be doubled after 24 hours.

In chronic bronchitis and asthma, numerous organisms have been used in the treatment of these conditions sometimes with great benefit. The difficulty lies in finding the causative bacillus and preventing secondary infections. The following organisms have been used: *B. influenza*, dose 10 to 100 millions; *M. catarrhalis*, 100 to 1000 millions; *B. septus*, 100 to 1000 millions; *Streptococcus hæmolyticus*, 10 to 100 millions.

TUBERCULINUM PRISTINUM, B.P.

(Tuberculin. Prist.)

Old Tuberculin

It is the concentrated filtrate from a fluid medium on which *Bacillus Tuberculosis* has been grown. Supplied in transparent, viscous fluid, yellow to brown in colour, odour like honey.

B.P. Dose—(For diagnosis) $\frac{1}{100}$ to $\frac{1}{10}$ minim or 0.001 to 0.005 mil by subcutaneous injection. (Therapeutic) $\frac{1}{10000}$ minim gradually increased, or 0.000001 mil gradually increased, by subcutaneous injection.

ACTION AND USES

Tuberculin is used either for making diagnosis or for the treatment of tuberculosis. The following are the different diagnostic methods used, viz.—

Von Pirquet Test or Scarification Test.—The required amount (minute drop) is placed on the skin and the part scarified. In tuberculosis there is swelling and a red flush after 24 to 48 hours, when the reaction is called positive.

Subcutaneous Test.—This is done by injecting subcutaneously, and the presence of tuberculosis is indicated by local induration and redness. A febrile reaction with increase of sputum to any dose up to 0.001 c.c. means definite activity; no reaction to 0.01 c.c. excludes active disease. Reactions to about 0.005 c.c. are indefinite.

The tuberculous patient may react either locally at the site of the injection, focally with exacerbation of signs in the lesion, or generally by a rise of temperature. It is for the rise of temperature only that it is used in the subcutaneous test.* This test is more valuable in children than adults.

Intradermal Test (Mantoux).—This consists in injecting 0.1 mil of a 1 in 10,000 or 1 in 1000 dilution of tuberculin in normal saline. Positive reaction is indicated by the formation of a red flush with central thickening. The reaction appears between 6 to 8 hours, reaches its maximum in 24 to 48 hours. This test is very sensitive and is presumptive of active tuberculosis in children under five. In adults negative reaction excludes tuberculosis, but a positive reaction is not always indicative of active lesions.

The tubercle bacillus is said to consist of: (a) a protein part which only can make the uninfected body allergic, and

* Halliday Sutherland, *Medical Press and Circular*, 1934.

produce a reaction in the allergic body ; (b) a lipin part, which causes cell necrosis ; and (c) a carbohydrate part. *Purified protein derivative* obtained from standard tuberculin (Tuberculin P.P.D.) is now available and is used for testing by the intradermal method, the dose being 0.00002 mg., and failing a reaction, 0.005 mg. is then given. Positive reactions may be classified as follows :—

- + swelling from 5-10 mm. in diameter.
- ++ swelling from 10-20 mm.
- +++ swelling more than 20 mm.
- ++++ swelling and necrosis.*

For curative purposes the injections are given in very minute doses, and gradually increased according to the reactions, as evidenced by rise of temperature, and other local and general reactions. But this vaccine proved a failure owing to excessive toxicity, and Koch ground up the bacilli in saline solution and allowed the emulsion to stand for some hours. The upper layer, *Tuberculin ober*—T.O. he found contained the fever producing element ; the deposit—*Tuberculin ruckstand*—T.R. was comparatively free from this danger. This residue was well washed and made up in 20 p.c. glycerin, the present day T. R. on the market. Wright showed that the German school has been using too large doses, which was the reason of their failure. He used the tubercle bacillus dried and ground up in an emulsion with saline—*Tuberculin Bacillary Emulsion*—T.B.E. and there are two varieties on the market, *bovine* and *human T.B.E.* As it is almost impossible to count the bacilli owing to morphological variations, the dose is estimated in milligrams of dried bacillary substance.

The following may be taken as representing the present trend of opinion on the value of Tuberculin :—

(1) *Tuberculin* (T.B.E.) should be given in very small doses, 0.00000001 mg. and gradually raised, and should not exceed 0.001 mg.

(2) The dose should be controlled by general reactions, fever, pulse ; local reactions at the site of inoculation ; and focal reactions at the site of the disease. The dosage should not be increased if these reactions are excessive.

(3) The treatment is most useful in surgical tuberculosis of joints and glands due more often to the bovine type ; of limited value in chronic tuberculosis of the lungs and intestines.

(4) Tuberculin should not be employed in the acute stage of the disease.

Recently much attention is being paid to the prevention of tuberculosis, and the main principles in this direction are (1) destruction of the infection, and (2) increase of individual

* Long, Seibert and Aronson, *Tubercle*, 1935.

resistance. With this object in view the following methods have been advocated to obtain immunity, *viz* —

(a) *Injection of living virulent tubercle bacilli.* This was found to be too dangerous to try on human beings.

(b) *Use of avirulent tubercle bacilli.* The latest attempt to attain this object is by the injection of **B.C.G. Vaccine** (*Bacillus Calmette-Guerin*). This consists of bovine tubercle bacillus attenuated by 230 passages in 13 years on potato-glycerin and bile. In spite of varying experimental reports, B.C.G. vaccine injected subcutaneously give relative immunity for a time, but how long this lasts is not known.

It may be given by the mouth but the results have not been very successful. Subcutaneous injections sometimes give rise to cold abscess, but less when the dose is 0.03 to 0.02 mg. The effect of B.C.G. vaccine as summarised by Heimbeck is that it tends to produce a moderate immunity before the appearance of allergy manifested by positive Pirquet reaction. It is not strong enough to prevent infection, but prevents the infection from becoming malignant and renders it benign, so that it acts like a new dose of vaccine increasing the antibody to a point where it gives an allergic reaction.

THE CAUSES OF FAILURE OF VACCINE THERAPY

The commonest cause is due to the fact that the wrong organism is isolated. To avoid this two to three cultures on different media should be taken. If the benefit produced does not go on to cure, another culture should be made, *e.g.* in an acute eczema, at first only the *staphylococcus aureus* and *albus* can be isolated, when the acute symptoms subside and the eczema weeps serum, *streptococcus* may then be recovered from the serum. The dose may be too small, or too large. An individual factor may also be present, thus an adult with plenty of bone and muscle usually gives a good response, whilst the old and feeble are bad subjects for immunisation. Rarely one meets with individuals who are hypersensitive to these injections, for them the dose has to be very carefully and gradually increased, otherwise more harm than good will be done.

THE ABUSES OF VACCINE THERAPY

From what has already been said, vaccines should not be employed

(1) *In acute diseases, viz. pneumonia, septicaemia, erysipelas, and acute tuberculosis.*

(2) *When dead tissue, viz. necrosis or abscesses are present.* These conditions should be treated surgically, and repair hastened by the proper application of vaccines. Nobody would try to save a gangrenous leg by vaccine therapy, yet one has seen large psoas abscess, softened glands in the neck, sinuses with necrosed bone, given vaccines.

(3) *When the causative organism has not been diagnosed, e.g. the use of coli vaccines in an unknown fever, the blunderbuss vaccines employed for the treatment of chronic bronchitis, injecting non-pathogenic streptococci in rheumatoid arthritis.*

(4) *When the organisms are not in contact with the antibodies present in the blood, e.g. in superficial infections of the throat and nasal mucous membranes, the use of the acne bacillus in preventing comedones, etc.*

✓ PROTEIN THERAPY

Within recent years much doubt has been thrown on the specificity of the vaccines and sera used in the treatment of different diseases, since it has been found that a non-specific vaccine may sometimes be not only useful, but even act better than a specific vaccine in the treatment of a particular disease. Thus, it has been shown that some forms of gonococcus infections are greatly benefited by injections of other vaccines, *e.g.* typhoid vaccine. Upon this is based nonspecific protein therapy. It appears that the good effects observed by giving injections of peptone solutions, milk, etc., are due not so much to the presence of any specific substance, but possibly to the special kinds of foreign proteins which these injections may contain. Similarly normal horse-serum, sodium nucleinate, bacterial proteins and non-proteins like colloidal metals have been injected to provoke a reaction of the body's defensive mechanism.

The popular method of utilising protein therapy is by the injection of sterile milk, and the beneficial effects are due to the production of vaso-dilatation and consequent flooding of the diseased tissues with antibodies. Apart from milk various substances have been used to produce protein shock. They are (1) peptones in graduated doses in the treatment of bronchial asthma, urticaria, migraine, etc.; (2) non-specific vaccines, *e.g.* T.A.B. vaccine in acute and subacute arthritis, sciatica and general paralysis of the insane as a substitute for malarial therapy, and Coly's fluid in the treatment of malignant disease; (3) artificially induced diseases, *e.g.* malaria in the treatment of (G.P.I.); (4) blood and sera, *e.g.* auto-hæmotherapy in asthma, typhus, whooping cough and non-specific urethritis. This is done by injecting intramuscularly 5 to 10 mls of patient's own blood, and (5) vegetable and animal protein, *e.g.* pollen extracts.

Protein injections may be used therapeutically for the following purposes:—

1. *Desensitisation.*—It has been observed that certain individuals develop asthma, hay fever, urticaria, angioneurotic œdema, etc., due to their sensitiveness or idiosyncrasies to certain proteins. Whether it is the actual food that causes the above conditions, or whether the particular foodstuff which produces within the system an antifoed protein body to be is too sensitive, is however uncertain.

This sensitiveness to special proteins can be tested by different food products. The method followed is like doing multiple Von Pirquet's reactions, using the dried extracts in place of the tuberculin. It is generally done by scratching in regular sequence upon some surface of the body, generally the forearm, and into each successively is rubbed the product to which it is desired to test the sensitiveness of the patient. If the patient gives a strong reaction at one of the inoculated spots, it is regarded as evidence of his sensitiveness to this special substance.

Once the case is established, the patient is treated either by avoiding the particular food substance or by producing desensitisation by injecting either a specific protein (antigen) to which he is sensitive, or by a non-specific protein like peptone or milk. The initial dose should be very small to avoid any reaction. Subsequent injections are given weekly, increasing the dose with each injection.

2. Non-specific protein when injected parenterally is followed within a short time (generally from a few minutes to one hour) by a rise of temperature, chill, sweating and leucopenia followed by leucocytosis. There is an increase of atypical erythrocytes and blood platelets, increase of fibrinogen, globulin, thrombokinas, blood sugar, non-protein nitrogen content, proteolytic ferments. Finally it increases the permeability of the cell membranes and capillaries. These reactions are more evident after intravenous injection, and after intramuscular injection in susceptible persons. Coincidentally with

these changes there is an increase in the antibodies and an improvement in the general condition of the patient, and a subsidence of the pain and other symptoms. The improvement is often temporary, but some patients show permanent improvement.

Protein therapy has been found efficacious in **acute and sub-acute arthritis, gastric and duodenal ulcers**. Acute **iritis** and other diseases of the eye due to local infection improve with parenteral injection of milk. The usual dose is 5 c.c. boiled for 4 minutes, or any of the preparations available for the purpose may be used. Similarly intra-gluteal injections have been used in subacute and chronic **gonorrhœal arthritis**, sometimes with good results. **Urticaria, migraine** and attacks of **asthma** being due to hypersensitiveness to certain proteins, oral use of peptone is a simple and harmless method of checking these attacks. Injections of **Yatren-Casein, Lactolan, or Aolan** (sterile and toxin-free milk albumin) have yielded good results in gynaecological practice attended with chronic inflammation of the appendages.

Contra indications. -Uncompensated cardiac lesion, acute endocarditis and pericarditis. Alcoholism is an absolute contra-indication. It should not be used in generalised or chronic multiple infection of long duration.

PART V

RADIATION THERAPY

ULTRA-VIOLET RAYS

Light is caused by the periodic vibration or rotation of electrons, and is the result of waves of energy transmitted through the ether. The visible light rays of the sun are composed of seven primary colours, at one end of which are the red rays and at the other the blue and the violet. In addition to these there are invisible light rays. At one end of the visible spectrum are invisible rays known as the *infra-red rays* and at the other the *ultra-violet rays*. The ultra-violet rays are the chemical rays, so called from the chemical changes they produce when projected on a sensitive medium. They are invisible light vibrations, between 400 to 100 millimicrons in length. The infra-red rays include the dark heat rays.

The composition of the rays of the sun varies with the altitude and the purity of the atmosphere. In fact the atmosphere screens off the harmful radiations. The ultra-violet rays are easily destroyed or made ineffective by moisture, dust and organic matters present in the atmosphere. In pure air there are more ultra-violet rays, so that the more purified air of mountain may contain twice as much ultra-violet rays as that of the air of the plain.

The biological action of sunlight depends upon its intensity and power of penetration and absorption. An excess of heat rays is harmful, and it is to the preponderance of heat rays that the harmful effects of the tropical sun are due. Sunlight, as is well known, is essential to the well-being of all living beings, both animal and vegetable. But it is to the ultra-violet rays that most of the therapeutic effects of solar radiation are attributed.

The first effect of exposure is vaso-dilatation and oedema of the soft tissue, this acts as a counter-irritant and relieves congestion of the internal organs. After a latent period of four to eight hours there is erythema of the skin, although the patient may not feel anything at the time of exposure. The next effect is sterilisation of the superficial tissues. The short rays are strongly bactericidal, and these are filtered out by impurities in the atmosphere before the long rays. After a few exposures there is pigmentation of the skin which is much the same as that produced from exposure to sun's rays. This pigment protects the body against the ultra-violet rays, and after this is formed one can stand larger doses of the rays. The response of the skin to light varies, some skins being highly sensitive.

There is evidence that exposure of an infected area inhibits the growth of micro-organisms, probably by forming some germ-killing body in the infected tissue. The other important effect is the regulation of calcium metabolism (*see page 99*). Gates and Grant have shown that in partially parathyroidectomised animals irradiation had a definite influence in preventing tetany, and that there was a rise of serum calcium after a steep decline. It bears definite relation to body metabolism associated with parathyroid physiology, and in the absence of factors which light represents, an attempt to compensate is made by over-activity of the parathyroids.

A powerful ray alters the proteins of the skin, and these abnormal proteins when absorbed, give rise to allergic condition in the skin making it intolerant to light. The ergosterol of the skin is activated by these rays and acquires an *antirachitic property*.

Immense possibilities of treatment by Heliotherapy has been proved by Rollier, who exposed his patients to sun's rays in the Alps.

Indeed the ideal treatment for lupus, surgical tuberculosis and rickets is by Heliotherapy at a higher altitude, where a much greater intensity of direct sunlight can be borne. But owing to the climatic and other conditions that prevail it is not possible to practise direct sunlight treatment, except on a limited scale or in certain selected parts in India. Therefore the treatment by ultra-violet rays is done chiefly by artificial light, and electric incandescent and arc lights are largely used for the purpose. Electric lights possess properties similar to those of sunlight. The arc light is full of luminous rays but there is also a good proportion of the rays at the violet end of the spectrum and a fair amount of the ultra-violet rays. In the incandescent lamp the heat rays predominate, the ultra-violet rays are absent, being removed by the glass globe. Arons in 1892 was able to electrify mercury vapour and produce a light devoid of orange and red rays. Subsequently Cooper-Hewitt perfected this in a glass vacuum tube, so that when quartz is substituted for glass, the small amount of ultra-violet radiation given off by the incandescent lamp can be made available. The mercury vapour lamp, which is known as the "Kromayer lamp" is therefore largely used. This consists of a tube from which air has been exhausted and which is filled with mercury and mercury vapour.

The advantages of carbon arc lamp are: (a) the output of ultra-violet rays being small the chances of an overdosage are less and no harmful effects are observed; (b) for the same reason can be used for treating weak and debilitated patients in whom the use of mercury vapour lamp may be harmful; and (c) a large number of patients can be treated at the same time, since slight errors of timing are not attended with any signs of overdosage.

The disadvantages are: (a) consume a large amount of current and give off CO₂; (b) the electrode may burn unequally in open arc pattern; and (c) the output of ultra-violet rays being less the results are slow.

The ultra-violet rays only penetrate a short distance, the hæmoglobin of the blood acting as a red filter screen. Under compression from surface quartz applicators or other means, the depth of penetration is increased. It is important to note that these actinic rays do not pass through glass, paper, thin cloth or ointment, but will pass through sterile water. *Vita glass* permits wave lengths up to 2000 Angstrom units to pass through it.

The therapeutic applications of ultra-violet rays are many. Their power to cure surgical tuberculosis and rickets, to accelerate the healing of wounds and to improve the general health of weakly children has been well established. Many chronic skin diseases rebellious to other forms of treatment often yield good results when exposed to these rays, using the tungsten arc lamp. Lupus, rodent ulcer and X-ray dermatitis are successfully treated with these rays. Septic wounds, sinuses, and chronic ulcers heal quickly. Good results have been reported in the treatment of chronic articular rheumatism, myalgia, fibrositis and rheumatoid arthritis. In many depressed states of the health and neurasthenia, a brief exposure often gives a feeling of stimulation and a sense of well-being.

Method of administration. This varies with the type of lamp used, the depth and extent of lesion, the power of resistance, the idiosyncrasy, and the sex of the patient. An average distance of three feet with mercury vapour lamp, and of 18 in. or less with arc lamp is considered as the average standard. The starting dose should not be more than one minute for mercury, and two minutes for carbon arc lamp. The following points require careful consideration in all cases:—

1. The eyes of both the patient and the operator must be protected by suitable goggles. Ordinary tinted or smoked glass does not offer sufficient protection.

2. For other parts of the body not intended for exposure, ordinary clothing affords sufficient protection.

3. Children can stand relatively larger doses; women are more sensitive than men.

4. The exposure should be given once, twice or three times a week according to the condition of the trouble.

5. After continuous exposure for three months for half an hour at a time there should be a pause for several weeks.

Contra-indications.—The application is harmful to highly nervous and neurotic people and in various forms of neuritis, where it may do definite and irretrievable harm. The following conditions either contraindicate or require modification of the dosage ordinarily given:—

1. Extremely sensitive skin.

2. Arterio-sclerosis or advanced valvular diseases of the heart.

3. Active pulmonary tuberculosis with fever. A focus of early and latent phthisis may flare up into activity through injudicious use.

4. Acute illness.

5. A tendency to hæmorrhage. It should not be given in hæmoptysis or in those suffering from hæmophilia.

6. Chronic nephritis or quiescent appendicitis.

Untoward effects—The belief that ultra-violet radiation is beneficial in almost any condition and that it does no harm is a mistake. While it does good in some conditions it is injurious and positively harmful in others. A common effect of overdosing, apart from that of the skin, is sleeplessness, restlessness, lassitude, loss of weight and nausea. Exposure of an extensive surface lessens resistance to bacterial infection. Eczema and many forms of skin affections are aggravated by these rays, while senile cataract has been known to follow its use when proper protection has not been taken for the eyes. A case of severe burn followed by duodenal ulcer has been recorded.

RADIUM

Radium is an element of the strontium-barium group and forms four important salts, *viz.* bromide, chloride, carbonate and sulphate. It is constantly undergoing transformations into other substances, and becomes successively emanations of radium A, B, C, D, E, F. During these changes energy is radiated from the substance in the form of so-called *Alpha*, *Beta* and *Gamma* rays, upon the various effects of which its therapeutic action depends. Radium emanation is a gas which is scattered in the air. It is therefore put in sealed containers where emanation gradually accumulates until a maximum is reached when it is converted successively into different forms of the series. A sealed preparation of radium element or emanation emits the three types of rays, each of which has the following characters:—

The *a* rays travel at the rate of 18,000 miles a second, but they have very little penetrating power. As they cannot pass through a thin sheet of paper, glass, or the metal wall of the emanation containers, they have very little therapeutic value, except in the treatment of superficial lesions of the skin.

The *β* rays travel at the rate of 60 to 180,000 miles a second and penetrate about 8 mm. of tissue, but cannot penetrate over 2 mm. of lead or 1.2 mm. of brass.

The *γ* rays are vibrations of ether and are analogous to X-rays or ordinary light. These have greater penetrating power.

Therapeutically *Beta* and *Gamma* rays may be used either together, or singly, the other rays being excluded by suitable screening. Certain substances (lead, silver, platinum, etc.) offer resistance to the passage of the different radium rays and these are used as screens.

β radiation is used chiefly in the treatment of diseases of the skin and affections of the mucous membranes, and the exposure is

so regulated as to produce only definite surface radium reaction (Superficial Radium Therapy). Its action is much the same as cautery, diathermy or carbon dioxide snow.

Beta and *Gamma rays* are employed when dealing with malignant disease and morbid conditions of the pharynx and larynx, and other deep seated organs, *e.g.* the stomach, intestine, uterus, etc. (Deep Radium Therapy).

ACTION AND USES

Some believe radium to be the most expensive and efficient form of cautery as yet discovered, while others maintain that it has a marked selective action in destroying pathological tissues without affecting normal tissue. The effect varies with different growths and even in normal tissues.

Radium emanation if of sufficient intensity and acts for sufficient length of time has three distinct effects on the living cell, *viz.*—(1) Increase of cell activity with possibly associated proliferation; (2) arrest of cell activity; and (3) degeneration and destruction of cell. The effects are not apparent immediately after exposure. Generally 1 to 2 days or even 2 to 3 weeks pass before any change is observed. This latent period varies with the strength of the source of energy and the amount of filtration and protection used.

Because of its destructive effect on certain forms of tumour cells, the chief application of radium is found in surgery. Although it cannot replace surgery, some permanent cures of superficial cancer of the skin of the basal-celled type have been recorded when properly treated. Rapidly growing cellular types of malignant disease often show at least a temporary set-back. As a palliative in subduing hæmorrhage, relieving pain, arresting discharge and offending odour and in prolonging life at least temporarily, its value is undisputed.

It has been successfully used in rodent ulcers, epitheliomata of the skin and keloids, while some cases of successful treatment of tumours of the brain are also recorded. In lymphomas and Hodgkin's disease, application of radium reduces the size of the involved glands, but whether any permanent cure is effected is doubtful. Similarly improvement has been noticed in both simple and exophthalmic goitre.

Its use in the treatment of cancer of the rectum is followed by good results, but do not justify its use as a substitute for operation. The best results are obtained in epithelioma of the anus and in the low growths of the posterior wall. Its use in the carcinoma of the breast has been followed by remarkable results and it is now recognised that early cases can be treated as successfully by radium as by operation. In the treatment of carcinoma of the cervix uteri, "split doses" or repeated treatment at brief intervals as recommended by Heymann of Stockholm is generally followed. In borderline and inoperable cases, radium is the method of choice and gives better results than X-rays. In fibroma and fibromyomata of the uterus, its use has been attended with encouraging results.

METHOD OF APPLICATION

The main principle underlying all radium therapy is the correct estimation of dosage and exposure necessary to bring about the death of pathological cell without markedly affecting the function and vitality of the normal ones. An insufficient dose may act as a stimulus and thus aggravate the condition, while an over-dose may destroy normal tissue. The source of radiation should be standardised under the exact conditions in which it is to be employed. The duration, the amount of radio-active element, filtration, distance, and susceptibility of the skin and the general vitality of the patient demand careful consideration. The intensity and quality of the rays depend on the amount of radio-active substance, the distance from the patient and the filtration used, while the effects depend on

the rays absorbed by the tissue. The dose for surgical use is usually from 50 to 200 mg. For superficial skin lesions smaller doses are used, while for large deep-seated growths larger doses are necessary.

Methods of administration.—For therapeutic purpose radium may be applied in the following ways:—

1. *In platinum tubes or needles.*—This prevents the alpha and beta rays. Each tube contains 2 to 3 mg of radium with 0.5 to 0.8 mm. of platinum screening. This gives quite good results.

2. *Radon seeds.*—Radium emanation or radon is a gas soluble in water, which can be stored in small tubes or seeds. These seeds are minute needles of gold or platinum which contain minute glass tubes of radium emanation. These seeds are inserted in diseased tissues with special form of cannula and left permanently there. They are therefore of special use in the treatment of diseases of the abdominal cavity where one can be inserted and left inside, thus avoiding another operation. They cease to give off rays after ten days.

Acute constitutional symptoms follow surface and distance therapy with large quantity of radium, than with interstitial radiation. Malaise, headache, nausea, and diarrhoea are generally observed. Irradiation of the upper abdomen is often followed by more severe constitutional disturbance than of head, neck, or pelvis.

Local changes in those handling radium are chiefly due to *alpha* and *beta* rays, and produce blunting of sensation of the finger tips, paræsthesia and anæsthesia, thickness of the epidermis and chronic dermatitis. If injury is severe, healing rarely occurs; hair follicles, sebaceous and sweat glands disappear. Telangiectasis and pigmentary changes with chronic ulcerations may also take place.

The *constitutional disturbances* have been attributed to cellular destruction and consequent protein absorption. Patients already in toxic condition are more susceptible to radium sickness. The mechanism by which tissue destruction provokes these symptoms is not fully understood. They may be a form of anaphylaxis or may be due to diverse metabolic changes at different stages of irradiation.

The following points should be noted in the therapeutic use of radium, *viz.*—

- (1) That its intensity varies with the length of exposure. A short exposure causes stimulation of the tissues, a longer exposure inflammation, and a prolonged exposure destruction of the cells.

- (2) That healthy cells react to radiation in proportion to their rate of growth. Lymphatic organs, hair follicles, glands of the skin, testicles and ovaries are particularly sensitive and are easily destroyed; while cartilage, bone, muscle, connective and nerve tissues are resistant to radiation. Diseased cells are more readily destroyed than healthy ones.

- (3) That malignant cells and the cells of a more rapidly growing tumour are more easily affected by radiation than normal ones.

PART VI

✓ INDIAN INDIGENOUS DRUGS

Expectorants and Bronchial Antispasmodics

अधत

ADHATODA

Syn. - *Bakasa*, Beng. *Arusha*, Hind.

Source. The fresh and the dried leaves of *Adhatoda Vasica* (*Justicia adhatoda*).

Composition. - (1) *Vasicine*, a crystalline alkaloid (2) An *organic acid* (adhatodic acid). (3) *Ammonia*.

PREPARATIONS

1. *Tinctura Adhatodæ*.—Dried powder 2½ ozs., Alcohol (60 p.c.) q s to produce 1 pint by percolation. *Dose*—30 to 60 ms. or 2 to 4 mls.

2. *Syrupus Adhatodæ*. Can be prepared by adding 1 of liquid extract to syrup 8. *Dose*—60 to 120 ms. or 4 to 8 mls.

PHARMACOLOGY AND THERAPEUTICS

Externally. The leaves possess **insecticide** properties, and are used for blight on tea and other crops.

Internally. Both the leaves and roots are stimulant **expectorants** and **bronchial antispasmodics**. The root may be used as a substitute for *senega*. It is an excellent remedy for **chronic bronchitis**, **phthisis** and **bronchial asthma**. It acts by virtue of *vasicine* which relaxes the bronchial muscles by depressing the vagus endings (Chopra and S. Ghosh). The decoction of the root bark is frequently used by the people of this country in catarrh, mild fever and bronchitis. It is useful in mild forms of **pertussis**, especially when complicated with bronchitis. The leaves smoked in the form of cigarettes relieve **asthma**, as they evolve ammoniacal vapour when burnt. It forms a vehicle for cough mixtures and is largely used in the form of syrup.

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SAUSSUREA LAPPA

Syn. The Costus, Kut.

Source. The dried root of *Saussurea lappa*, with pungent aromatic odour and a pungent taste.

Composition. - (1) *Saussurine*, an alkaloid. (2) An aromatic oil. (3) Resin, tannin, bitter substances, inulin, etc.

ACTION AND USES

Kut has been used in India as a **tonic**, **antiperiodic** and **aphrodisiac**. The essential oil is an antiseptic and is eliminated by the genito-urinary tract which it stimulates. It is possible that the aphrodisiac effect is due to local irritation. *Saussurine* causes **relaxation** of the **bronchial muscles** partly by direct action on the muscle, and partly through the vagus (Chopra). The essential oil acts as an expectorant while excreted through the bronchial mucous membrane. It is therefore largely used in the treatment of **bronchial asthma**, and as an **expectorant** in the form of the liquid extract (30 to 60 ms.) either alone or with other expectorants like potassium iodide. It is also used as a **carminative** and **diuretic**.

✓

Laxatives

BELAE FRUCTUS

Source.—The fresh half-ripe fruit of *Albizia Marmelos*.

Composition.—(1) *Marmelosin*, the important active principle (2) Tannin (3) *Pectin*. *Mucilaginous principles*, sugar, etc.

PREPARATIONS

1. *Extractum Belæ Liquidum*—1 in 1 *Dose*—60 to 120 ms or 4 to 8 mls.
2. *Decoctum Belæ*, B.P.C.—Bael fruit small pieces 8 oz, boiling water *q.s.* 20 oz. *Dose*— $\frac{1}{2}$ to 2 oz or 15 to 60 mls.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The pulp of the ripe fruit is a laxative, and is valuable in spastic and chronic constipation. The pulp may be taken itself or may be made into a sherbet by soaking in water and then straining it. A little sugar may be added if required. The unripe pulp roasted, or a decoction made from the unripe slices dried in the sun (*Bael suti*) is astringent and is therefore used in mucons diarrhoea and dysentery. As a demulcent and mild laxative the ripe fruit may be used during convalescence from dysentery and early stage of sprue. The compound or dietetic bael powder (powdered pulp 1, arrowroot 1) may be used in the same class of cases. The ripe pulp is very serviceable in obstinate catarrhal diarrhoea, chronic dysentery and certain forms of dyspepsia characterised by alternate constipation and diarrhoea.

The root-bark of the plant is a mild febrifuge and enters into the composition of the "ten roots"—*dasha mula*—so frequently prescribed in mild fevers by the *Kavraj*es.

✓ Drastic Purgatives

TU PETHU

Syn—*Tew* Beng. *Tarbad*, Hind.

Source.—The dried root and stem of *Ipomœa Turpethum*

Composition.—(1) A resin, *Turpethin* The root contains 5 to 10 p.c. (2) A fatty substance (3) A volatile oil (4) Albumin, starch, yellow colouring matter, lignin, salts and ferric oxide.

Dose—5 to 20 gis or 0.3 to 12 gm.

PREPARATION

1. *Tinctura Jalapæ Composita*.—Jalap 80 gm, scammony resin 15 gm, turpeth 10 gm, alcohol (60 p.c.) *q.s.* to 1000 mls. *Dose*.—30 to 60 ms or 2 to 4 mls

PHARMACOLOGY AND THERAPEUTICS

As a purgative it is equal to *jalap* and superior to *rhubarb*; it has moreover a great advantage over both these drugs in that it is free from nauseous smell and taste. It also acts very efficiently when given alone. It is often necessary to give it in larger doses than *jalap*, but this is no disadvantage. It has been in use in India as a cathartic from a very early date. When combined with chebulic myrobalans, it is useful in dropsy. The usual method of administration is to rub down about a drachm of the root or stem with water and add to it some rock-salt and ginger, or sugar and black pepper.

KALA ANA

Syn—*Pharbitis* Seeds

Source—The dried seeds of *Ipomœa hederacea*

Composition—*Pharbitis*en, a resin, about 8 p.c. It resembles the resin of *jalap* (*convolvulin*), and corresponds to it in chemical properties. Fixed oils, 12 p.c, mucilage, tannin.

Dose—30 to 45 gis or 2 to 3 grms

PREPARATIONS

1. *Pulvis Kaladanæ Compositus*—Kaladana, 3, acid potassium tartrate, 6; ginger, 1 *Dose*—10 to 60 grs or 0.6 to 4 gm.
2. *Tinctura Kaladanæ*.—1 in 5 *Dose*—30 to 60 ms. or 2 to 4 mls.

KALADANAE RESINA

Syn.—Pharbitisin.

Source.—A mixture of resins obtained from Kaladana. In brownish opaque fragments, translucent at the edges, brittle, breaking with a resinous fracture of a disagreeable odour, specially when warmed.

Dose.—2 to 8 grs. or 0.12 to 0.5 gram.

PHARMACOLOGY AND THERAPEUTICS

The action and uses of kaladana and its resin are the same as those of jalap (*see* page 359), but it is a milder remedy. In small doses it is a gentle purgative, but in large ones, especially in the form of Pulv. Kaladanæ Co. it has a drastic action and can be used with benefit in all cases of dropsy.

✓ **Diuretics****BOERHAAVIA DIFFUSA**

Syn.—Punarnava.

Source.—The fresh or dried leaves.

Composition. (1) An alkaloid *Punarnaine*, 0.01 p.c., (2) potassium nitrate, 0.2 p.c.

PREPARATION

1. **Extractum Punarnavæ Liq.**—1 in 1 of alcohol. Made with fresh or dried leaves. **Dose.**—30 to 60 ins. or 2 to 4 mils.

PHARMACOLOGY AND THERAPEUTICS

Punarnava has been used in India as a remedy for dropsy from time immemorial. But only recently a thorough investigation of the drug has been done. Intravenous injection of the alkaloid produces a distinct and persistent rise of blood-pressure and a marked diuresis. The diuresis is chiefly due to the action of punarnavine on the renal epithelium, and partly to the rise of blood-pressure. The presence of a large amount of nitrate of potassium contributes to the diuresis when the liquid extract is used. It is very valuable in cases of dropsy due either to cirrhosis of the liver, or when associated with kala-azar, and ascites due to chronic peritoneal conditions. It is not of much value in cardiac dropsy or in chronic nephritis when given alone, but combined with other diuretics it increases the amount of urine. It loses its action after a few days when its use should be stopped.

✓ **Urinary Antiseptics****CUBEBAE FRUCTUS**

Syn.—Cubebs; *Kabab chhu*, Beng.

Source.—The dried full grown unripe fruits of *Piper Cubeba*.

Composition. (1) The volatile oil, 10 to 18 p.c. (2) *Cubebin*, a neutral body. (3) A resin containing *cubebic acid*. (4) A *fatty oil*, Gum.

Dose.—30 to 60 grs. or 2 to 4 grms.

PREPARATIONS

1. **Oleum Cubebæ.** A pale green, greenish yellow or colourless oil, smelling of cubebs, distilled from cubebs. **Dose.**—5 to 20 ms. or 0.3 to 1.2 mils.

2. **Tinctura Cubebæ.**—1 in 5. **Dose.**—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY

Externally.—The action of cubebs depends upon the oil and the resin which it contains. It is a rubefacient to the skin.

Internally. Gastro-intestinal tract.—Here the action of cubebs resembles that of pepper. In small doses it is a stimulant, stomachic and carminative, and in large doses it impairs digestion. In still larger doses it causes gastro-intestinal irritation.

Respiratory and genito-urinary tracts.—Like many oleoresins, cubebs enters the blood and is carried to different tissues and organs, upon which it acts more or less like copaiba. It stimulates the secretions of the mucous membranes of the respiratory and genito-urinary passages and renders them aseptic. It also stimulates the action of the kidneys, and to some extent that of the skin. It is therefore a diuretic and genito-urinary antiseptic.

Elimination—It is chiefly excreted in the bronchial secretion and urine, and is probably found in the latter in the form of a salt of cubebic acid, which may be precipitated by HNO_3 . Many of the specific germs are destroyed by the products of the volatile oil as they pass out.

THERAPEUTICS

Internally.—Unlike copaiba, cubebs is often used in the form of lozenges or inhalation to relieve cough, cold and sore-throat. On account of its specific action on the genito-urinary passages, it is largely employed with copaiba, in acute or chronic gonorrhœa, gleet and cystitis.

Prescribing hints.—The powdered cubebs may be given in lozenges, cachets, or as a paste with copaiba, and the oil in capsules, or in emulsion, often with copaiba, buchu, etc.

Antiperiodics

ER ERIS

Syn.—*Daruhandra kasta*, Beng *Darhald*, Hind

Source—The dried stem of *Berberis aristata*.

Composition.—The chief alkaloids are (1) *Berberine*, and (2) *Oxycanthine*, tannin, resin, gum, etc.

PREPARATIONS

- 1 *Tinctura Berberidis.*—1 in 10. *Dose*—30 to 60 ms or 2 to 4 mils
- 2 *Ext Berberis*—An impure watery extract from the wood and bark of several species of berberis sold in the Indian bazaars under the name of *Rasot*, which can be purified by dissolving it in alcohol (90 p c) and evaporating it to a pilular consistence. *Dose*—30 to 60 grs. or 2 to 4 gims.
3. *Berberine Carbonate, Hydrochloride, Phosphate and Sulphate*, are yellow crystals more or less soluble in water. *Dose.*—1 to 5 grs. or 0.06 to 0.3 gm.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Being a mild local astringent, *rasot* is employed with benefit as a pigment around the eyes in acute and chronic ophthalmia. Gupta and Dikshit have shown that berberine in dilution of 1 in 80,000 is toxic to *Leishmania tropica*, in which condition it has been used successfully either in the form of *Rasot*, or berberine sulphate 1 c.c. of a 1 to 2 p.c. solution may be infiltrated into the margins of the sores by means of a fine hypodermic syringe, once a week.

Internally—Berberine is a stimulant to the gastro-intestinal tract, and acts as a stomachic tonic in small doses. It is a diaphoretic and antiperiodic and has been used in the treatment of malaria, either alone or in combination with quinine. It is doubtful, however, whether it has any specific effect on the parasites, and the results have been disappointing. It however helps to expel the parasites into the peripheral circulation and acts as a provocative agent in the diagnosis of malaria.

Given intravenously the alkaloid causes a fall of blood-pressure from dilatation of the splanchnic vessels and cardiac depression.

ALSTONIA

Syn.—Dita Bark *Saptaparna*, Sans. *Chatim*, Beng. *Chatian*, Hind.

Source.—The dried barks of *Alstonia scholaris* and of *Alstonia constricta*.

Composition.—The bark contains many alkaloids, the chief being *ditamine*, *echotamine* or *ditaine* from the *dita bark* (*A. scholaris*), and *Alstonine* and *porphyrosine* from the bark of *A. constricta*.

PREPARATIONS

1. Infusum Alstoniæ 1 in 20. Dose — $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.
2. Tinctura Alstoniæ 1 in 8. Dose —30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

The bark is an astringent, tonic, antiperiodic and anthelmintic, being considered very useful in chronic diarrhœa, advanced stages of dysentery and catarrhal fevers. Ditaine paralyses the motor nerve-endings in mammals. It has been used successfully in the treatment of malarial fever. Dr. Sharp used the bark of *A. constricta* in certain conditions of typhoid fever, and influenza after its febrile stage and considers it to be an excellent tonic possessing the combined properties of quinine and strychnine.

PICRORHIZA

Syn. *Kutki*, *Kutki*, Beng., Hind. (*Katuka*, Sans.)

Source. The dried rhizome of *Picrorhiza Kurtoa*.

Composition. (1) Bitter glycoside, *Picrorhizin*, yielding as its decomposition product *picrorhizin* and *dextrose*. (2) Cathartic acid. (3) Gum, etc.

Dose. 10 to 30 grs. or 0.6 to 1.2 gm. as a tonic; 45 to 60 grs. or 3 to 4 gms. as an antiperiodic.

PREPARATIONS

1. Extractum Picrorhizæ Liquidum—1 in 1 of alcohol (60 p.c.). Dose —15 to 60 ms. or 1 to 4 mls.
2. Tinctura Picrorhizæ.—1 in 4. Dose 30 to 60 ms. or 2 to 4 mls.

PHARMACOLOGY AND THERAPEUTICS

The root is bitter and stomachic and is often used whenever a bitter is indicated, as in dyspepsia and neuroses of the stomach and bowels. It is an antiperiodic, and is used in malarial fever in place of, or with, quinine. Because of the presence of cathartic acid it acts as a gentle cathartic when given alone, and in large doses acts as a purgative. As a remedy for bilious fever *kutki* is often combined with various aromatics and neem bark.

✓ Volatile Oils

BETEL

Syn. — *Pan*, Beng. *Pan*, *Tumbuli*, Hind.

Source. The leaves of *Piper Betle*.

Composition.—(1) Two aromatic oils, light and heavy, which treated with caustic potash yield *charicol*, a phenol having powerful antiseptic properties. (2) An alkaloid, *arabene*, with properties somewhat allied to cocaine. (3) *Betel phenol* (chavibetol), a phenol.

PHARMACOLOGY

Externally.—Dry betel-leaf has no action. Fresh betel leaf is a gentle stimulant to the skin, due to the volatile oil it contains.

Internally.—When chewed, the fresh leaf, because of the presence

of volatile oil, is a mild sialagogue, allays thirst and dryness of the mouth. It also removes foulness of the breath. Reaching the stomach the juice produces a sensation of warmth and acts as a mild stomachic and carminative, at the same time gives a feeling of well-being. It is a mild astringent and expectorant. The warm juice is considered a febrifuge. Too much chewing of *pan* blunts hunger, probably because of the presence of the alkaloid arakene. If taken in excess it may cause intoxication somewhat similar to that of alcohol.

It has been suggested that it excites sexual impulses but there is no definite proof.

THERAPEUTICS

Externally.—As an easily available domestic remedy, betel leaf is used for various purposes. Smeared with mustard oil or *chunam* (hydrated slaked lime) and warmed, it is applied to the temples in headache, to the neck in sore-throat, to swollen glands to promote their absorption, and to the breasts to check the secretion of milk. In catarrhal and pulmonary affections of children, the leaves smeared with oil and warmed are applied in layers to the chest as mild counter-irritants. The leaves may be similarly employed in hepatitis, orchitis, ovaritis, etc. The Bengal betel leaves are valuable in these cases. They are used as dressings for foul ulcers, or as substitutes for oiled silk or gutta-percha tissue. The juice is sometimes dropped into the eye in ophthalmia or into the ear (warmed) to relieve earache. The stalk of the leaf smeared with oil is introduced into the rectum in constipation of infants.

Internally.—The people of India chew prepared *pan* which is made by wrapping slices of areca nut (*Areca catechu*) with a proportionate quantity of catechu, *chunam* (hydrated slaked lime) and spices in betel leaves. This combination is very efficacious in ulcerated and spongy gums, and as a digestive adjuvant in dyspepsia. Prepared *pan* is an excellent masticatory for removing the after-taste of bitter and nauseous drugs. The juice may be given as an expectorant in colds and cough, or as an antipyretic in the catarrhal fever of children.

LEU AJOWAN

Syn.—Ptychotis Oil *Jowaner tel*, Beng. *Ajowan tel* *উজোয়ান তেল*

Source.—The oil distilled from the fruit of *Carum ajowan*.

Characters.—Colourless, odour and taste of thyme, sp gr. 0.910 to 0.930. If cooled to 15 °C should yield not less than 40 p c. of crystalline *thymol*, known in the Indian bazaars as *ajowan ke phool*.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The action and uses of the oil resemble those of thymol (see page 545). The fruit when chewed removes the nauseous taste of drugs and the oil corrects the griping of purgatives. *Omum water* or *ajowan ke arak*, distilled from the fruits, is a valuable carminative and antispasmodic in colic and flatulent dyspepsia. *Ajowan* is often chewed with *pan*, or taken with salt for indigestion.

PS AL A C YLIF LIA

Syn.—*Babchi*, Beng.

Source and characters.—The seeds are brownish-black, 2 mm. long, flattened and oblong. Odour, aromatic; taste, bitter, pungent.

Composition.—An essential oil, a fixed oil, and a resin.

ACTION AND USES

It has been used as a remedy for *leucoderma*, and within recent years its use has been revived by Acton, who found the oleo-resinous

extract (which contains most of the volatile oils) a suitable preparation, which is rubbed over the diseased patches. It is of no use in leucoderma of syphilitic origin.

Astringents

MYROBALANU

Syn.—Chebulic Myrobalans *Haritaki*, Beng. *Harā*, Hind.

Source.—The dried immature fruits of *Terminalia Chebula*.

Composition.—(1) *Tannic acid*, about 20 to 40 p.c. (2) *Gallie acid*. (3) Resin, etc.

Dose.—30 to 60 grs. or 2 to 4 grm.

PREPARATIONS

1. **Unguentum Myrobalani.**—1 in 5 of benzoinated lard.
2. **Unguentum Myrobalani cum Opio.**—7.5 p.c. of opium

PHARMACOLOGY AND THERAPEUTICS

These fruits were highly extolled by the ancient Hindu physicians as powerful astringents, stomachics, and tonics. The finely powdered fruit forms an important ingredient of tooth powder and forms a valuable remedy for spongy and ulcerated gums. Paradoxical as it may appear the dried unripe fruit acts as a gentle laxative. One or two fruits taken daily at bed-time keep the bowels very regular, giving one or two evacuations in the morning. On account of the astringent and aperient properties, myrobalans, especially the smaller variety (*Jangi haritaki*), are very useful in diarrhoea and dysentery. Owing to the large amount of tannin which they contain, they are of great service as lotions and injections and may be substituted with advantage for galls. The ointment is a valuable application in piles. They may also be chewed with benefit to remove the after-taste of nauseous drugs.

KURCHI CORTEX

Syn.—Conessi Bark. *Kurchi*, Beng. *Kutaja*, Sans.

Source.—The dried bark of *Holarrhena antidysenterica*.

Composition. The seed and the bark contain three alkaloids (1) *Kurchicine* or *Conessine*, an amorphous powder, soluble in water and alcohol and in dilute acids. (2) *Holarrhentine*. (3) *Kurchins*. Also contains tannin.

Dose.—2 to 5 grs. or 0.12 to 0.3 grm. in tablets.

PREPARATIONS

1. **Extractum Kurchi Liquidum.**—1 in 1 of alcohol. **Dose.**—60 to 120 ms. or 4 to 8 mils.
2. **Infusum Kurchi.**—1 in 10 of boiling water. **Dose.**—1 to 2 ozs. or 30 to 60 mils.
3. **Kurchi Bismuth Iodide.** **Syn.**—*Anabin*; *Kurchibine*.—Contains total alkaloids 27 p.c., bismuth 22.8 p.c., iodine 50.15 p.c. **Dose.**—4 grs. twice a day for two weeks.

ACTION AND USES

Kurchi is a well known remedy for the treatment of dysentery both acute and chronic. It acts by virtue of the alkaloid *kurchicine* which has a specific action on *E. histolytica*. Before the value of ipecacuanha was recognised in dysentery it was the only remedy extensively used in India. It may be given alone, either in the form of liquid extract or as fresh infusion, or may be combined with small doses of castor oil, extract of bael, or decoction of ispaghula, or the seeds (*indrajab*) may be given in the form of powder with powdered ispaghula seeds. *Kurchicine* may be used subcutaneously in $\frac{1}{2}$ to 1 gr. doses, but as it depresses the heart and makes it irregular it

cannot be used intravenously. It has the advantage over emetine in being useful also in **bacillary dysentery**. It has no effect on the pregnant uterus in therapeutic doses and therefore may be given safely during pregnancy (Chopra). Kurchi-bismuth-iodide is now used in cases of chronic intestinal amœbiasis with better results than with pure kurchi preparations, and has the advantage over similar preparation of emetine in not being a depressant. The alkaloid may be used in the same conditions and is free from any cumulative effect. Sometimes flushing of the face and extremities, giddiness, and buzzing of the head occurs, but these pass off on reducing the dose or stopping it for a few days. It may be given in capsules or as tablets. (Acton and Chopra).

Kurchicine is an antiperiodic and may be used by the mouth (2 to 5 grs.) with benefit in cases of dysentery complicated with fever.

✓ Anthelmintics

UTEAE SE INA

Syn.—Butea Seeds, *Palas Bu*.

Source.—The seeds *C. B. Berz; ganssa*

Composition.—Fat 18 p.c., albuminoid substances 19 p.c., and glucose. The fat exists in the form of *moodooga* oil

PREPARATION

1. **Pulvis Buteæ Seminum**—The kernel dried and powdered, freed from the testa after soaking in water. *Dose*.—10 to 20 grs. or 0.6 to 1.2 gm.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The seeds are powerful anthelmintics for round-worm and may be used as a substitute for santonin, followed as usual by a dose of purgative.

✱ CUCU ITAE SE INA PRAEPA ATA (Bengali)

Syn.—Red Gourd Seeds, *Pepo* ✓ Melon Pumpkin Seeds; *Bilati Kumrar bij*, Beng *Mitha-kamu ka bij*, Hind (मीठा कदु के बीज).

Source.—The prepared fresh ripe seeds of cultivated plants of *Cucurbita maxima*

Composition.—(1) A resin, fixed oil 30 p.c., sugar, starch, etc

Dose.—1 oz or 30 grms.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Both the seed and the oil are efficient anthelmintics for tape-worm. The former is best given bruised with a little water or milk on an empty stomach early in the morning, followed by a simple purgative at 10 A.M., the latter in $\frac{1}{2}$ oz. doses repeated at an interval of 2 hours and then followed by an aperient.

E ELIA खान डिंग (Marathi)

Syn.—*Buanga* Beng *Baberang*, Hind. *Vadanga*, Sans.

Source.—The dried fruit of *Embelia Rubes*, and of *Embelia robusta*.

Composition.—(1) *Embelic acid* or *embelin* 2.5 p.c. (2) An alkaloid *Christembine*, resin and tannin

Dose.—1 to 4 drs or 4 to 16 grms (in powder).

PHARMACOLOGY AND THERAPEUTICS

These berries are considered a valuable anthelmintic for tape-worm, and may be used in powder or as infusion (without straining). The taste is not unpleasant and the directions are the same as those given for the administration of melon pumpkin seeds. ✱

Demulcents

ISPAGHULA

Syn.—Spigel Seeds. *Isaphgul*, Beng

Source.—The dried seeds of *Plantago arata*

Composition.—(1) *Mucilage*, 1 in 20 of water forms a thick tasteless jelly. (2) *Fibred oil* and albuminous matter

Dose.—45 to 150 gis. or 3 to 10 grms. (in powder).

PHARMACOLOGY AND THERAPEUTICS

Externally. The bruised seeds, moistened with water, form an excellent, emollient poultice, and can be used for the same purposes as linseed.

Internally. Isaphgul is a demulcent and mild laxative acting like agar-agar by virtue of its bulk. Like the seeds of *Plantago Psyllium*, it is used for correcting constipation. Two to three teaspoonfuls of powdered seed taken at bed-time with a little sugar and water give one or two clear evacuations without any griping in the morning. When soaked in water (1 in 40) it forms a mucilaginous mass which acts as a protective layer over the intestinal mucous membrane, and is used as a domestic remedy in acute and chronic dysentery. The mucilage also inhibits the growth of bacteria in the intestine and adsorbs toxins, thus preventing their absorption. It is often combined with bruised *kurchi seeds* (*Holarrhena antidysenterica*), commonly known as *Indrajah*, the dose is 5 grs. every two or three hours, and this combination will be found to yield most encouraging results. The decoction is also used as demulcent in cough and sore-throat, and formed into a sherbet (seeds, sugar and water) it is largely used as a cooling beverage in gonorrhœa, when it acts as a mild diuretic and soothes the irritation of the urethra during urination.

AGROPYRUM

Syn.—Triticum ; Couch Grass

Source.—The dried rhizome of *Agropyrum repens*, freed from remains of leaves and rootlets.

Composition. (1) *Triticin* resembling inulin. (2) *Glucose*, *mucilage*, *mannite*, *inosit*. No starch.

PREPARATIONS

1. **Decoctum Agropyri.**—1 in 20 Dose— $\frac{1}{2}$ to 2 ozs. or 15 to 60 mls.
2. **Extractum Agropyri Liquidum.**—Dose.—60 to 120 ms. or 4 to 8 mls.

PHARMACOLOGY AND THERAPEUTICS

Internally. It is a demulcent and diuretic, being largely employed in cystitis and irritation of the urinary passages. The decoction well diluted may be employed as a diluent. Only the fresh rhizome possesses these properties, the dried one is inert.

✓ Cardiac Tonic

TERMINALIA ARJUNA

Syn.—Arjuna ; *Arjun*.

ACTION AND USES

The bark of this tree possesses a reputation of being a valuable cardiac tonic and is extensively used in this country for all sorts of cardiac troubles and complications. The bark was subjected to careful analysis in the *Pharmacological Laboratory of the Carmichael Medical College* and was found to contain (a) *tannin* about 12 p.c. mainly of pyrocatechol nature ; (b) soluble salts of *calcium*, *mag-*

nesium and aluminium, 22.4 p.c.; (c) an organic acid of high melting point; (d) Colouring matter, and (e) sugar.

The reputation of the drug and the fact that it is extensively used and advertised as a cardiac tonic led us to make a careful investigation of its action on animals. The observations of Chopra were negative, although it is possible that the high calcium content may have some effect on the cardiac muscle. Experiments made with liquid extracts obtained from the reputed manufacturers and prepared in the laboratory show that it causes a fall of blood pressure in intact animals even in very small doses; while larger doses cause death of the animal from stoppage of the heart. On isolated heart the beats were rendered weaker and eventually the heart stopped from direct action on the cardiac muscle. These findings are directly opposite to the general belief. Further work is necessary to substantiate these observations.

✓ Antiseptic

A A I ACHTA IN ICA

Syn.—Neem Bark, Margosa Bark.

Source.—The dried bark of the stem of *Melia azadirachta*.

Composition—(1) A bitter amorphous resin (2) *Margosine*, a bitter alkaloid.

(3) Margosic acid

PREPARATIONS

1. Infusum Azadirachtæ Indicæ.—1 in 100 Dose.— $\frac{1}{2}$ to 1 oz. or 15 to 30 mls.
2. Tinctura Azadirachtæ Indicæ.—1 in 10. Dose.—30 to 60 ms. or 2 to 4 mls.
3. Margosic Acid.—A mixture of fatty acids of the oil derived from the seeds.
4. Sodium and Potassium Margosates.—Valuable in combating infections of diverse nature in any form of skin affections. Injections are said to be useful in *leprosy*.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The leaves in the form of a decoction or poultice are largely employed to stimulate foul and indolent ulcers to a healthier action. The decoction is also used as an antiseptic lotion or general bath in many skin diseases. Obstinate ulcers have been cured by neem-poultice. Weeping eczema quickly heals if a cold poultice of the bruised leaves is applied and allowed to remain till it drops off.

The oil extracted from the seeds is a valuable local stimulant, antiseptic and bactericide. Alone or in combination with *chaunmoogra* oil or *gurjun* balsam, it is considered to be an effective application in *leprosy*. Injections of *margosates* and the local application of the acid have been found to be of greater value in the treatment of *leprosy* and *syphilitic* conditions than the oil.

Internally.—The bark is a bitter tonic, astringent and antiperiodic, the astringent properties residing in the outer layers. Before the introduction of quinine into this country, the bark either in powder (1 dr.) or in concentrated decoction, was largely employed in *malaria*. Its decoction is employed even now in many cases of *malarial fevers* where quinine fails to effect a cure, or as a tonic during *convalescence*. The root bark possesses *anthelmintic* properties.

✓ PART VII ✓ PHARMACY AND DISPENSING

GENERAL DIRECTIONS

1. The dispensing room must be well *lighted* and well *equipped* with every necessary article, furniture and apparatus for compounding and dispensing purposes.

2. **Pure drugs of the best quality** are to be used, and preparations are to be made in strict accordance with the *official* and other *recognised methods*.

3. **Bottles are to be duly labelled.**—Those containing corrosive fluid must have *enamelled inscription*, or names engraved on glass. Bottles containing **poisonous** substances must bear an extra label—“**Poison**” at their shoulders. It is a good plan to have also the *doses* printed on the labels.

4. **Poisonous drugs** must be kept within a separate glass case under lock and key.

5. **The counter and the apparatus** for compounding and dispensing must be kept scrupulously clean, in good order, and ready for immediate use. Always clean and put away every article in its proper place after use.

6. **Testing of drugs** must be done occasionally so as to ensure their purity and strength. Substances like vegetable extracts, spirit of nitrous ether, hydrocyanic acid dilute, etc., require occasional looking after.

7. **Corks of good quality** should be used. Cracked, old, rotten and soiled corks should be rejected. The practice of pressing corks between the teeth should never be indulged in. Fit a cork before pouring the medicine into the bottle.

8. **Evidence of slovenliness** as regards externals does not encourage faith as to the care with which the contents have been dispensed.

9. **Prescription reading.**—Read through a prescription calmly and rapidly, without creating any suspicion in the mind of the presenter, but noting at the same time any inconsistency either in dosage or in combination.

10. **Consultation with the prescriber** must be arranged without delay, whenever possible, if there is any **poisonous** or **unusually large dose**, or a grave incompatibility in a prescription. The dispenser should on no account alter a physician's prescription without his sanction.

11. **The directions** on the label should be written first of all before the medicine is dispensed. At the same time the prescription should be copied in the copy-book, noting afterwards any peculiarity of compounding or dispensing. If the directions are in Latin, the dispenser should give their English translation. In India, the directions should be written in the familiar language of the place when the medicines dispensed are meant for those who cannot read English.

12. **Labels** should be neatly and distinctly printed without much flourish, and their margins carefully trimmed. “**Poison**,” “**Shake the bottle**,” “**Not to be taken**” and other accessory labels are best placed on the **shoulder** of a bottle. If affixed at the foot, the fingers holding the bottle may cover them, or a hurried patient may overlook them. The colour of labels for liniment and lotion ought to be different from that of mixture and powder. Orange-red and dark-yellow for the former and white for the latter may be used. Sometimes the labels for liniment and lotion are printed with red on white paper.

13. Bottles for dispensing mixtures should be of different colour from those used for liniments and lotions. Amber-coloured or uranium bottles are best suited for silver nitrate lotions, and blue bottles for liniments. Bottles covered with blue paper can be used for silver lotions, when uranium or amber-coloured bottles are not available.

14. The dispensing of two prescriptions simultaneously should never be attempted. But if an infusion is to be made the dispenser may set it on, noting on a bit of paper the time and the substance, and placing it between the cover and the pot.

15. The position of a prescription during dispensing must be such that the dispenser can read it while dispensing. This can be best accomplished either by fixing it to a hook on a counter-shelf, or by holding it between the index and the middle fingers of the left hand.

16. Manipulation.—Be expeditious in manipulation. Finish tying, sealing, labelling and wrapping as quickly as possible. The holding of powder envelopes between the lips, the handling of drugs, the stirring of mixtures with the fingers are to be avoided.

17. The final reading of a prescription is essential before the medicine leaves the hands of a dispenser, so as to make a revision of his work. If there is any doubt, always begin where there is none.

18. Graduations of bottles must be accurate. Want of symmetry of the bore makes a great deal of difference. Blown lines of graduation are generally wrong. Paper graduation is the best, but it must be done by hand in each case. Mark-papers should either be notched or lined equidistantly, but in either case the number of doses should be put down in figures on the label.

19. Repetition of prescription.—If a prescription contains such drugs as are likely to produce a cumulative effect, or a habit, as strychnine, arsenic, lead, digitalis, opium, etc., the dispenser should warn the patient against repeating it for a lengthened period without the knowledge and sanction of the prescriber. To prevent indiscriminate renewals of medicine containing poisonous ingredients, the physician should write "*non-repetatur*" or some similar direction on his prescriptions.

WEIGHING AND MEASURING

1. Scale.—An upright fixed beam and scale with a movable glass pan should be used. If a hand scale is used, hold it firmly by the left hand, never lift it too high above the counter, and judge the weight as much by the indicator as by the position of the scale. A delicate scale should be used for weighing minute quantities of powerful drugs; such as strychnine, hyoscyne, arsenic, etc.

2. Corroding substances.—Substances which corrode or act on the brass should be weighed upon glass pans. Crystallised acids, iodine, carbonate of ammonia and similar salts should never be weighed on brass pans.

3. Soft or sticky substances, such as soft extracts, confections, ointments, etc., should be weighed on a piece of paper spread over the right pan, after placing a corresponding piece of equal weight on the left along with the weights. Scrape the medicine by a spatula from the paper after weighing.

4. No guesswork in weighing or measuring is allowed. Every drug must be either weighed or measured.

5. Label upwards.—In pouring out liquids, always keep the label of the bottle upwards in order that it may not be spoiled by the trickling down of the drops of liquid left on the lip of the bottle.

6. Minim measure.—From a few drops to a drachm, the liquid should be measured in a minim glass. The true level of the surface of the liquid in a minim glass is the midway between the highest point close to the glass and the lowest at the centre.

7. Lip drops.—The drops that hang from the lip of a bottle out

of which a liquid has been poured, should be caught upon the bottom of the stopper, before putting it back into the mouth.

8. **How to drop** Before permitting drops to fall into any mixture, the dispenser must allow a few drops to fall on a separate vessel till he is confident that he has a perfect control over dropping. If he is not sufficiently skilful, let him measure the drops into an empty glass until he is satisfied that he has obtained the correct number.

9. **Volatile liquids**, such as, ether, chloroform, nitrite of amyl, dilute hydrocyanic acid, etc., should always be measured instead of dropped. A solution of 10 or 20 per cent. may always be kept in stock for measuring out small quantities when ordered.

10. The size of drops varies considerably, and therefore it is safe to give *minims* where *guttae* are ordered. Thus, chloroform dropped from an ordinary phial will require 150 to 300 drops to one fluid drachm.

When 'drop' is used, it should be measured by means of a tube which delivers in 20 drops 1 gm. of distilled water at 15°C.

11. **Division of a grain or a minim** is best accomplished by triturating or mixing the weighted or measured quantity with sugar of milk or any liquid excipient, and dividing the mixture as ordered. For instance, suppose that 24 pills are ordered, each containing $\frac{1}{4}$ grain of strychnine hydrochloride. The total amount in the 24 pills will be $4\frac{1}{2}$ grain, therefore weigh out 1 grain of the salt and triturate it with 4 grains of milk sugar, making 5 grains in all. Then 4 grains of this mixture will contain $\frac{1}{5}$ grain of strychnine hydrochloride. Take this amount and destroy the remainder.

WATERS

1. **Camphor water.** 2 ozs. of water dissolve only $\frac{1}{2}$ gr. of camphor. The easiest way of making a good camphor water is to mix flowers of camphor with coarsely powdered glass, enclose and tie the mixture in a muslin bag and suspend it by a thread into the water from the cork. A good solution is obtained sooner by moving the bag up and down two or three times a day.

By dissolving 150 ms. of spirit of camphor in 40 ozs. of water, camphor water may be quickly obtained.

2. **Chloroform water** is made by the simple shaking of chloroform in water.

For the preparation of **aromatic waters**, see page 16.

DECOCTIONS

1. **Drugs** should be coarsely powdered or sliced before they are boiled in water for 5 minutes or longer. If the comminution is too fine some sediment deposits. The drugs should always be put in cold water before boiling.

2. **Decoction pots** should be enamelled or tinned and covered. A false bottom made of tinned or silver gilded copper wire half an inch or more above the bottom should be used to prevent imparting a fusty odour to the decoction from the particles of the drug adhering to the bottom of the vessel during boiling.

INFUSIONS

1. **Drugs for infusion** should not be too finely comminuted.

2. **No other water than distilled water**, boiling or cold, is to be used.

3. **Suspension of drugs** is essential. A muslin bag containing the drug can be suspended by a thread from the lid of a covered pot, or a Squire's or Maw's infusion pot may be used.

4. **Uniform temperature**, as far as possible, should be maintained.

5. **Hard spring water** does not give a good colour, as the extractive matters are not well dissolved by it.

6. **Infusions** should be made fresh and these are now named in

the Pharmacopœia as fresh infusions as distinguished from concentrated infusions introduced in the new B.P., which after dilution resemble the fresh infusions. The concentrated infusion of digitalis is not sanctioned in the new B. P. and should not be used, as it is inactive.

EMULSIONS AND MIXTURES

Emulsion, as its name implies, is a liquid externally resembling milk, the milkiness being due to the suspension of resinous or oily bodies in water, by means of an adhesive substance known as the *emulsifier* or *emulgent*. Emulsion therefore is a mixture of two liquids which are insoluble in each other. The emulsifier helps the insoluble substance to remain finely divided or broken up in the form of globules which do not coalesce again to form a separate unmiscible fluid.

Emulsions are prescribed (a) to help administration of oily substances which will not mix with water; (b) to help easy absorption of the oily substance which is presented in a finely divided and dispersed state in some vehicle; and (c) to make it more palatable.

1. The first fundamental rule in the compounding of a mixture is to avoid chemical decomposition taking place among its ingredients, unless such is the implied intention or the express order of the prescriber.

2. Distilled water should be used in compounding. Tap or other waters produce a considerable change in mixtures owing to the presence of traces of calcium and magnesium salts. For example, Tinct. Cardam. Co. produces a brilliant crimson colour with tap, and a reddish-brown with distilled water. Tinct. Lavand. Co. gives a bright mixture with distilled, and a muddy one with tap water. Ordinarily the word "aqua" means tap water. If the prescriber wants distilled water to be used he should write "aqua destillata".

3. Order of mixing.—It is not the spirit of practical pharmacy to mix the ingredients in the order in which they are written in a prescription. The dispenser should exercise his own judgement in determining the best method of effecting a combination.

It is a good plan first to pour in the tinctures and spirituous fluids as they are measured, next add syrups and essences, and lastly fill up the bottle with the vehicle.

4. Poisonous drugs such as arsenic, strychnine, perchloride of mercury, hydrocyanic acid dilute, etc., should be separately dissolved and then added to the mixture last of all, immediately before corking the bottle. In this way you avoid the possibility of putting them in twice over.

5. Mortar and pestle should never be used if the ingredients are easily soluble. Dispense syrups and fluid preparations in such an order that the vehicle will finally rinse out the measure glass.

6. Shaking.—All mixtures should be briskly shaken before labelling, to ensure a thorough incorporation of the ingredients.

7. Heat should not be used to help the solution of salts when they will not entirely dissolve in cold water, for they are sure to crystallise on cooling. Suspension is the best method under such circumstances.

8. Wholly or partially soluble vegetable drugs, especially which contain tannin, should be mixed with earthy and metallic salts in largely diluted solutions.

9. Gelatinous mixtures.—Some mixtures become gelatinous on keeping, due to the growth of an organism called *viscous ferment*. An addition of 20 per cent. of alcohol to the mixture prevents this.

10. Chemical reaction.—If there is a chance of a chemical reaction taking place, the ingredients which are likely to act with one another, should be freely and separately diluted or suspended, before mixing. The mucilage of acacia always suspends the precipitate uniformly, and to some extent retards or modifies the chemical decomposition.

11. **Froth.** - Sometimes a lot of froth rises as the result of shaking, especially if the mixture contains vegetable solutions, thus preventing the bottle from being filled or corked. A few drops of alcohol remove this.

12. **Insoluble powders** are sometimes prescribed in a mixture. These fall into two groups: *diffusible* and *indiffusible*. Powders such as rhubarb, chalk, compound powder of jalap, heavy and light magnesium oxide and carbonate, quinine sulphate are diffusible and should be triturated with a small quantity of water in a mortar to produce a thin paste, before mixing with the vehicle. No suspending agent should be used by the dispenser unless it is found that equal dosage of the substance is not possible without one. Most of the insoluble powders are easily diffusible and do not require a suspending agent. In any case "shake the bottle" label should be used.

A substance is regarded as *indiffusible*, when it will not remain evenly distributed in the vehicle for a long period to ensure uniformity of the dose. They are: acetanilide, acetylsalicylic acid, barbitone, benzoic acid, betanaphthol, bismuth salicylate and oxychloride, chlorbutol, resinous substances, quinine salicylate, quindine sulphate, salicylic acid, etc. These require a suspending agent.

13. **Medicinal filtrates** produced in a mixture should not be filtered, but suspended. But if any foreign particles float on a clear solution, they should be removed either by straining or by filtration through wetted cotton or tow plugged lightly into the neck of a funnel. All mixtures depositing a sediment should bear the label "shake the bottle."

14. **Mucilage** should be recently prepared, but it can be kept ready made for some time provided that the bottle containing it is full up to the neck and properly sealed.

15. **Oils** are best emulsified either by rubbing them up with gum or by mixing them with an alkali, or with both. Copaiba is well emulsified with gum and alkali. Essential oils are best emulsified with tragacanth powder in the proportion of 10 grs. for every ounce, or yolk of egg.

16. **Scale preparations** in a mixture are either to be dissolved in a mortar with warm water or poured into the bottle with the vehicle and shaken briskly. If poured in a dry condition into the bottle, and the water or vehicle added afterwards, a sticky mass cakes at the bottom.

17. **Volatile ingredients in a mixture.** - Volatile drugs such as ammonia, ether, chloroform, hydrocyanic acid, etc., should never be mixed with hot fluids, and should always be added last of all, after the vehicle has been poured into the bottle. Care should be taken that sufficient space is left for the requisite quantity of the soluble ingredient. As soon as this has been added, the bottle must be tightly corked and well shaken.

18. **Resinous substances** should first be finely powdered and triturated with mucilage of tragacanth and finally the vehicle is added. They may also be dissolved in alcohol and dispensed in the same way as resinous tinctures.

SUSPENDING AND EMULSIFYING AGENTS

Suspending agents are often necessary to keep insoluble substances in a state of suspension so that each dose should contain a reasonably correct proportion of the compound. Suspending agents are also necessary when liquid preparations containing resinous substances, are used in a mixture, as these may form precipitate and adhere to the side of the bottle. If the prescriber does not order any such agent the dispenser should use his own judgement in deciding whether any suspending agent should be used. The following substances are commonly used as suspending agents, *viz.* acacia, tragacanth, or mucilage of acacia or mucilage of tragacanth, glucose, or syrup.

Mucilage of acacia should be used in the proportion of 1 dr. for each fluid ounce of the mixture. It however has the disadvantage of making mixtures sometimes lumpy, as for instance with bismuth salts, where tragacanth is more preferable and should be used in the same proportion.

There are many *emulsifying agents* and they are almost invariably colloidal substances and thus remain in a state of extreme subdivision in which state its surface area is enormously increased. This state of subdivision demands expenditure of energy, and this energy becomes stored up on the surface of the particles as surface energy, and more finely divided the substance, the greater is its surface area and, consequently, greater its surface energy with greater power to adsorb other substances to its surface.

The emulsifying agents are :—

Acacia powder.—The formation of a good emulsion depends upon right proportion of oil, water and gum. The usual rule is to use one part of powdered gum acacia for every four parts of fixed oil. For volatile oils the proportion is half the quantity of gum as oil. For making emulsion with substances containing oleoresins like copaiba or male fern the proportion should be equal quantity of each.

Powdered gum tragacanth is inferior to acacia, as the oil globules are larger than acacia emulsion and therefore the emulsion with tragacanth is not so white. Gum tragacanth is used more for emulsifying volatile oils and less for fixed oils. The proportion being 10 grs. of the gum for every ounce of the oil. It is often used along with acacia to increase viscosity of the emulsion.

Yolk of egg is largely used for emulsifying cod-liver oil. Its emulsifying power is twice that of powder acacia. 4 dr. will emulsify 4 oz. of fixed oil and 2 oz. of volatile oil. It has the advantage over gum emulsion in that it does not separate on the addition of acids, salts, glycerin or syrup. If however the egg-emulsion is kept for long it undergoes putrefaction and imparts a bad odour to the emulsion. Sometimes a little benzoic acid, or 5 p.c. alcohol is added as a preservative.

Alkalies.—The hydroxides of potassium, calcium, ammonium and sodium are generally used. They form soaps by combining with the fatty acids contained in most of the fixed oils of vegetable origin. Volatile oils which do not contain any fatty acid cannot be emulsified with alkalies. Lime water and ammonia are however not used for emulsions intended for internal use. They are largely used for liniments and substances meant for external application.

Soaps.—These are best emulsifying agents for lotions, liniments and other preparations for external use.

Saponins.—These occur in certain substances and form a large amount of froth when shaken with water, similar in appearance to the froth produced when soap is shaken with water. The drugs which contain most saponins are quillaia and senega and the most convenient sources of these saponins for dispensing purposes are the tinctures of the respective drugs. Since both these substances have a therapeutic action of their own they should not be used for making emulsions for internal use unless especially ordered.

Casein and mucilage of starch are also used as emulsifying agents.

MIXTURES AND EMULSIONS OF SPECIAL DRUGS

1. **Acacia** in a mixture is best added in the form of mucilage, which should be freshly made.

2. **Almond Oil** does not emulsify well with mucilage or powdered gum, but a small quantity of liquor potassæ or carbonate of potassium without mucilage answers well.

3. **Ammoniacum, Myrrh and Guaiacum** should be triturated first with a little water or some similar vehicle so as to form a thin paste. These do not require a suspending agent as the gum present in these

is sufficient to suspend the resin. The resulting mixture may be strained through muslin.

4. **Ammonium Carbonate** should be dissolved in a cold vehicle, only translucent pieces being used. Those portions which have effervesced are wanting in strength.

5. **Benzoic acid** should be powdered before mixing. If there is a tincture in the formula it should be dissolved in it, and water added gradually with shaking.

6. **Bismuth Carbonate** and **Subnitrate** are often prescribed in a mixture without any suspending agent. They should first be triturated in a mortar with some of the vehicle to form a paste and then the water should be added to adjust the volume. They are easily diffusible and do not ordinarily require any suspending agent. If any suspending agent is used, *acacia* should be avoided for reasons explained on page 716. Bismuth subnitrate is chemically incompatible with potassium bicarbonate or sodium bicarbonate, producing a large quantity of carbonic acid gas when mixed in a mixture. The gas must be allowed to escape by gentle heat before bottling, otherwise the bottle may subsequently burst or the cork be suddenly blown out. An equivalent quantity of bismuth carbonate may be substituted as the finished mixture contains the same. Bismuth salts and iodides produce bismuth oxyiodide which gives a brownish red colour to the mixture though therapeutically it is harmless.

7. **Borax** powdered and rubbed up with mucilage makes a soft, jelly-like mass. But a limpid mixture may be obtained by mixing freely diluted mucilage with a solution of borax in warm water.

8. **Butyl-chloral Hydrate** forms oily compounds with alcohol, insoluble in water. Dissolve in glycerin and warm water. **Chloral hydrate** behaves in the same way, and is decomposed by alkalis, liberating chloroform.

9. **Caffeine Citrate** forms a syrupy liquid when mixed with three times its weight of water; on addition of more water, caffeine hydrate is precipitated. This is again redissolved on further dilution.

10. **Camphor** in a mixture is treated with three times its weight of alcohol, in the same way as resinous tinctures, *i.e.* dissolve it in alcohol first and then treat as a tincture. *Acacia* is a better suspending agent.

11. **Chlorate of Potassium and Hydrochloric Acid.** Sometimes a formula composed of potassium chlorate, hydrochloric acid, and water comes to the dispenser for dispensing. Here the object is to make a solution of chlorine, and is best fulfilled by adding the acid directly to the salt, corking the bottle for a while before adding water, so as to make a solution of chlorine in water.

Chlorate of potassium with syrup of iodide of iron liberates *free iodine* which has proved fatal.

12. **Cod-liver Oil** is well emulsified by the following method. Place powdered tragacanth in a dry mortar and triturate a little of the oil, then add the yolk of an egg and the oil and stir briskly, adding water as the mixture thickens, and lastly mix flavouring oils and water alternately, with constant stirring, avoiding frothing. The mixing of lime water 1 to 5 with cod-liver oil greatly facilitates its emulsification, and reduces its tendency to cause eructations. Lime water and *acacia* gum emulsify cod-liver oil just as the yolk of egg.

13. **Copaiba Balsam** can be well emulsified by rubbing it with about its own weight of powdered gum *acacia* and liq. potassæ. The resin acids combine with caustic potash and form a soap-like substance which helps emulsification.

14. **Ether** should never be mixed with hot liquids, and must be added last to a mixture.

15. **Ferri Sulphas** soon gives a rusty colour to a solution from the production of ferric hydroxide, which is retarded by adding an acid.

16. **Glycerin** is used as a sweetening agent for mixtures, especially

those that contain perchloride of iron. It is also used as an appropriate solvent for, and a preservative of the pancreatic and peptic ferments. It prevents gelatinisation of kino in tinct. kino, and also to a certain extent prevents and retards chemical changes and precipitation in a mixture.

17. Iodine is very sparingly soluble in water, but iodide of potassium helps solution to the extent of three-quarters of its own weight. Salts of ammonia also increase its solubility by the formation of a soluble salt, ammonium iodide. Some essential oils such as oils of peppermint and fennel, chemically combine with iodine. Strong solution of iodine with solution of ammonia, or with ammoniated camphor liniment, precipitates iodide of nitrogen, which is a most dangerous explosive (see Explosive Combinations, page 64).

18. Morphine Salts should not be dissolved by heat, for at a temperature above 104°F. their solutions turn yellow or brown.

19. Paraldehyde is soluble in water in the proportion of 1 in 10. If it is present in a mixture in excess of its solubility it should be emulsified with tragacanth powder.

20. Phenacetin in a mixture requires careful treatment. It should be first finely powdered and then mixed with pulv. trag. co. in the proportion of 2 to 5 grs. for every ounce of the mixture, and then the vehicle added with trituration in a mortar. The same procedure should be followed for acetanilide.

21. Phenazone is sometimes a troublesome drug to deal with in a mixture. It is rather a free base, and gives precipitate with tannin, alkaloids and many other substances. Thus, with alkaline salicylates it forms *salipyrin* (insoluble); with ferric chloride, *ferripyrin* (orange red); with free iodine, *iodopyrin* (insoluble); with chloral hydrate, *hypnal* (insoluble), etc.

22. Potassium Iodide is decomposed by acids, liberating free iodine, which may produce fatal results. This also happens when potassium iodide is mixed with tincture of perchloride of iron.

23. Quinine Salts.—The following points in respect of the mixing of quinine salts should be noted:—

(a) It produces an *insoluble salt* when added to a strong mineral acid; the acid should be freely diluted with the vehicle before the alkaloidal salt is mixed.

(b) When it is prescribed with spirit of nitrous ether, tinctures, ether, or any spirituous liquids along with glycerin or syrup and water, the quinine is to be first dissolved in the undiluted spirituous mixture and then glycerin or syrup added, and lastly the vehicle is gradually mixed. If no mucilage is ordered it may be added to prevent quinine from adhering to the sides of the bottle.

(c) The sulphate should not be dissolved in diluted hydrochloric or nitro-hydrochloric acids unless so ordered.

(d) When ordered with bark or any other substances containing tannic acid, it deposits a precipitate of tannate of quinine which should not be filtered.

(e) No acid should be added by the dispenser to make a solution if it is not prescribed. The quinine is then to be rubbed up in a mortar with a little mucilage and diffused in water, or added to the vehicle in its crystalline state, with "shake the bottle" as a direction. The former is the better method.

(f) Quinine salts are *incompatible with alkalies*, such as bicarbonates, carbonates, hydrates, sp. ammon. aromat., etc. They should be suspended and diluted *separately* before mixing; a small quantity of mucilage will make a better mixture.

(g) Ammoniated solution of quinine gives a precipitate when diluted with water, but the addition of a little mucilage ($\frac{1}{2}$ dr. to 1 oz. of mixture) suspends it.

(h) With liberated chlorine, quinine salts yield a yellow solution, i.e. when added to the chlorine mixture mentioned in para 11.

(i) Mercuric chloride, throws down a poisonous precipitate, which can be dissolved by diluted hydrochloric acid. Glycerin and gum also retard to some extent chemical reaction.

(j) Donovan's solution too behaves in the same way, but an admixture of glycerin and mucilage prevents to some extent chemical changes.

(k) When it is ordered with salicylates in a mixture, an ugly-looking mass, salicylate of quinine, forms inside the bottle which refuses to flow out. The mixture may be improved by rubbing mucilage with quinine and gradually mixing the salicylate dissolved in a large quantity of water, and agitating very briskly.

(l) Neutral solution of quinine and iodide of potassium do not react chemically, unless there is an acid present, free or liberated, in which case iodine is set free.

(m) The growth of fungus in a solution of quinine is prevented by the addition of a 5 per cent. solution of alcohol or a trace of chloroform.

24. **Spirit of Nitrous Ether** turns *acid* due to the fact that the ethyl nitrite becomes hydrolysed on keeping with formation of free nitrous acid and should therefore be made *alkaline* before being mixed with iodides or bromides, otherwise free iodine or bromine will be liberated and will darken the mixture. It can be kept permanently alkaline or neutral by dropping a few crystals of potassium bicarbonate in it.

25. **Salol** when combined with other salts in a mixture falls to the bottom in a somewhat granular form; this is prevented by adding compound powder of tragacanth in the proportion of 2 to 5 grs. for every fluid ounce of mixture.

26. **Strychnine** in a mixture containing alkalies is precipitated to the bottom of the bottle, and fatal results may follow the swallowing of the last dose. Bromide and iodide of potassium, liq. hydrargyri perchloridi and liquor sodii arsenatis all throw down insoluble precipitates of strychnine compounds.

27. **Tannic Acid** should be dissolved in pure distilled water, as tap water makes the solution opalescent. It precipitates alkaloids in solution and gives with iron an inky colour. Alkalies give precipitates, and turn the mixture brown to black. Mucilage makes it flaky.

28. **Vegetable extracts** should be carefully *rubbed* in a warm mortar with a little water till a soft paste is obtained, with which the vehicle is to be gradually mixed. If they are resinous rub them with two or three times their weight of powdered acacia in warm water, and then gradually mix with the vehicle when cold. *Ext. Filicis* may be triturated with its own weight of powdered acacia, and water added gradually with constant stirring.

PILLS

1. In making a pill-mass, the following points should be observed:—

(a) Put the substance (powder) prescribed in smallest quantity into the mortar first and triturate it with the next smallest (if it is powder), add the next, again triturate, and so on.

(b) Toxic substances (*e.g.* alkaloids and arsenic) should always be triturated well with double their weight of a hard powder (*e.g.* lactose), if there is none in the pill constituents, before adding the other ingredients gradually.

(c) Potent extracts which are prescribed in the pill should not be treated as excipients, *e.g.* *Ext. Nucis Vom.* gr. $\frac{1}{8}$ with *Pulv. Aloes* gr. 2, and *Pulv. Ipecac.* gr. $\frac{1}{8}$. Here rub the extract with the ipecacuanha, add a little of the aloes, again triturate, and continue thus until the extract is equally divided throughout the whole.

(d) Essential oils should be treated like No. (c). Thus in the case of *Pil.*

Aloes, the oil of caraway should be triturated lightly with the powdered soap (the oil being added gradually); then aloes, trituration, aloes trituration, etc.*

2. **Pills under one grain** should be made up to 1 grain by the addition of liquorice powder or sugar of milk. Fractions of a grain of such **powerful drugs** as strychnine, perchloride of mercury, arsenic, etc., should be intimately triturated with sugar of milk, and then made into pill-mass with suitable excipients.

3. **Pills liable to crumble** will keep their shape for a reasonable time if some fibrous materials, such as liquorice powder, paper pulp or lycopodium are added to the mass. If the pill-mass is too soft, it should be hardened on a hot plate, but if the ingredients are hard and brittle, they should be massed in a warm mortar. When the pill-mass contains dry vegetable powders some minutes must be allowed for the absorption of moisture before rolling.

4. **The same spatula** should never be dipped into the extract pot after it has been used to scrape the pill-mass from the tile, pestle and mortar.

5. **To prevent sticking together**, cinnamon or liquorice powder, mixture of starches, powdered French chalk are used. Pills containing hygroscopic and volatile ingredients should be varnished or coated and then dispensed in a well-stoppered or corked bottle. Pills for silvering should never contain glycerin.

6. **Substances that are decomposed by iron**, such as silver nitrate, copper, and bismuth salts, corrosive sublimate, and calomel, ought not to be mixed in an iron mortar, or scraped by an iron spatula.

7. **Crystalline salts soluble in water** should be very finely powdered, and massed with glycerin of tragacanth and some inert powder. Before silvering, they must be varnished with tolu and dried. Glycerin of tragacanth is the best excipient for insoluble salts.

8. **Essential oils**.—Soap and sometimes soap and powdered liquorice root make a good excipient. Wax is to be avoided. When there is much essential oil, the addition of liquor potassæ helps greatly.

9. **Potent Drugs**.—*To diffuse* potent drugs as atropine or strychnine, add a minute quantity of glycerin before massing.

10. **Scale preparations** should be finely powdered with a palette-knife instead of triturating in a mortar before massing. Use lanolin, kaolin, or mass rapidly with rectified spirit.

EXCIPIENTS

An excipient is a substance, either solid or liquid, added to bind the ingredients of a pill-mass into a plastic and adhesive mass. If none of the ingredients in the pill are suitable for producing a pill-mass, then it is necessary to add an excipient. The selection of a suitable excipient in these circumstances is done by the dispenser, which however requires experience. The following excipients are commonly used:—

1. **Acacia in powder** is a good excipient when judiciously used. It however makes the pill hard. With calomel it makes a regular cement. Combined with equal quantity of tragacanth it is better than acacia alone, and is known as Pulvis Acaciæ Co. It is frequently combined with syrup of glucose. It should not be used with wax, fats or oils, or with creosote.

2. **Alcohol** softens resinous substances, but the mass should be quickly rolled, otherwise it will crumble.

3. **Calcium Phosphate** in minute quantities gives a pilular consistence to greasy substances and essential oils when soap is not admissible. It is a good desiccant.

4. **Castor oil**, with or without soap, is a good excipient for making camphor pills.

5. **Compound decoction of aloes** is a good excipient for pills con-

* Chemists' and Druggists' Diary, 1898

taining aloes. It should not be used when the pills contain any substance which is incompatible with carbonate of potassium.

6. **Extract of gentian** though commonly used is not particularly adhesive and is dark in colour.

7. **Glycerin** keeps pills soft, but it is very hygroscopic. The addition of one-third of its weight of water overcomes its hygroscopic property. It is useful for pills liable to become hard.

8. **Glycerin, mucilage of acacia, water and alcohol** in equal parts make a good general excipient.

9. **Glucanth** consists of powdered tragacanth 1, glycerin 3, water 1, syrup of glucose 1. It is useful where glycerin of tragacanth is unsuitable on account of the large quantity of glycerin.

10. **Syrup of liquid glucose** contains liquid glucose 1, syrup 2, and is a serviceable excipient.

11. **Kaolin ointment** is useful for massing oxidisable and reducible ingredients; but has no advantage over lanolin with which it may be combined.

12. **Lanolin** may be used in massing certain scale preparations. Being non-oxidisable it may be used to mass potassium permanganate or silver nitrate with prepared kaolin.

13. **Liquorice or marshmallow** in powder are absorbent and give elasticity to the soft mass. They are useful for pills containing oils or phenol.

14. **Proctor's paste** consists of powder tragacanth 60 grs., glycerin 180 ms. and water 90 ms. The paste improves by keeping. It is an all-round good excipient.

15. **Resin ointment** is used for scale preparations, but wool fat is better.

16. **Soap powder** is the best excipient for vegetable powders, extracts and gum resins. It neither hardens nor crumbles. It should not be used for masses containing acids, acid salts, metallic salts, and substances containing tannin.

17. **Tragacanth powder** gives in small quantities solidity and elasticity to a soft mass; more so when the compound powder is used.

18. **Water** should be used with caution. It is a good excipient for masses containing gum or soap and makes a good pill with powdered opium.

19. **Wax** is not much used now for it makes pills indigestible, though it makes a beautiful pill-mass with camphor, creosote, phenol, and most of the essential oils.

Ince's Precautions. The excipients to be avoided are:—

(a) Those incompatible with any of the ingredients of the pill-mass. Thus, confection of roses must not be used to make iron pills; acetic extract of colchicum must not be stiffened with magnesia.

(b) Those which make the pill either too hard or too soft.

(c) Those which unduly increase size.

ROLLING, CUTTING AND ROUNDING OF PILLS

Having prepared the pill-mass to proper consistency it should be rolled out on a pill tile with a spatula to the required length for the number of pills ordered by bringing it along side of the scale in the tile. Before cutting the mass into pills, it is a good plan to weigh the whole mass to see that it corresponds to the total weight of the ingredients, a precaution against careless weighing. When a large number of pills are to be prepared the rolling is done in a pill cutting machine (*see* fig. 26) by putting the mass or cylinder on the rolling board and rolling it with the under surface of the cutter by moving it with two hands backwards and forwards. It is important that the pill pipe should be uniform in thickness and perfectly cylindrical, care being taken that the ends do not taper out thin. The pill pipe when ready should be brought along side the scale on the machine to

see that it fits the number of divisions corresponding to the number of pills into which it has to be divided. The dispenser being satisfied brings the pill pipe with his finger on to the grooved part of the machine. The cutter with the grooved surface downwards is

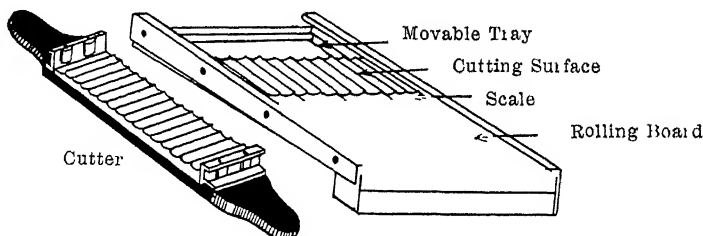


FIG. 26.—PILL MACHINE

pressed on the pill mass with both hands, and with a few jerking movements the pills are cut through and pushed into the removable tray. It is better to put some inert powder (liquorice root or French chalk) to prevent adhesion of the pills. If the pill mass is properly prepared and the operation successful no further treatment is necessary; but the track of the machine will be visible on the pills and therefore these require finishing to make them perfectly globular. This is done by placing the pills on a dusted slab and rolled with a pill rounder or finisher. These are shallow, circular, boxwood trays not deeper than the pills which one wants to roll.

PILLS OF SPECIAL DRUGS

1. Aloes is best made into pills with a minute quantity of compound decoction of aloes, which has a great solvent power, or with syrup of liquid glucose. Aloin is massed with glycerin of tragacanth.

2. Antipyrin makes a good pill with glycerin of tragacanth.

3. Argenti Nitras and Argenti Oxidum.—The nitrate decomposes in the presence of organic substances and should be rubbed to a fine powder with twice its weight of kaolin and massed with paraffin ointment, resin ointment or kaolin. The oxide parts with oxygen readily with creosote, ext. gent., etc. It should be massed with kaolin ointment.

4. Bismuth salts are best made into pills with glycerin of tragacanth.

5. Butyl-chloral Hydrate makes a good pill-mass with equal parts of powdered acacia, tragacanth and syrup, or glycerin of tragacanth.

6. Calcium Sulphide should be triturated with lactose to increase its weight if necessary, and massed with powdered acacia, tragacanth and glycerin. The pills should be varnished to protect from decomposition from the air.

7. Camphor should be powdered first with a few drops of alcohol, and after the evaporation of the spirit, use compound powder of acacia and mass with syrup of glucose.

8. Camphor Monobromata should be triturated with Pulv. Trag. Co. and massed with Proctor's paste.

9. Carbromalum is made into a pill with glycerin of tragacanth.

10. Cinchophen makes a pill with compound acacia powder, 2 p.c. of tartaric acid and syrup of liquid glucose or may be made with soap and glycerin of tragacanth.

11. Chlorbutol with acacia and syrup of glucose.

12. Citrate of Iron and Quinine can be made into a pill by the addition of rectified spirit and rolling the mass quickly, or use kaolin and lanolin.

13. Codeine can be massed with half its weight of powdered liquorice and glycerin of tragacanth.

14. **Copaiba**, when massed with carbonate of magnesia, makes a very hard pill which is insoluble in the intestinal secretions. If it be made into an emulsion with gum, and be set aside for twelve hours, after adding 1 part of magnesia levis to every 10 parts of the balsum, it may be converted into a good pill-mass by the addition of a minute quantity of borax, and such a pill is soluble. Phosphate of calcium also makes a good pill.

15. **Creosote** with powdered curd soap gr. 1 and powdered liquorice gr. 2 for each minim makes a good mass. **Guaiacol** should be treated like creosote.

16. **Emetine** and **Bismuth Iodide** pill is made with acacia and tragacanth. The pills should be keratin coated or salol varnished.

17. **Ferri Sulphas**. The granular sulphate forms a good pill with glycerin of tragacanth and a little powdered sugar of milk. When 5 gr. are used for each pill, it is better to use the dried salt of which 3 gr. equals 5 gr. of the undried salt. Liquid glucose makes excellent excipient for dried salt.

18. **Ferrum Redactum**.—First make a fine powder, add liquorice and mass with glycerin of tragacanth.

19. **Gallic Acid** and **Tannic Acid** make good pill-mass with glycerin of tragacanth.

20. **Hydrargyrum c. Creta** can be massed with glycerin of tragacanth. It should never be vigorously triturated in a mortar, as the mercury may separate.

21. **Hydrargyri Perchloridum** should be finely triturated with lactose and made into a pill with compound powder of acacia and syrup of liquid glucose. Calomel pills are also made in the same way.

22. **Ichthammol** is first mixed with tragacanth and then massed with liquorice.

23. **Menthol**, **Thymol**, **Camphor**, etc. or substances which become oily should be mixed with half the quantity of powdered curd soap and $\frac{1}{4}$ the quantity of beeswax and then massed with powdered liquorice root.

24. **Pepsin** can be massed with a mixture of equal parts of glycerin, syrup and water by quick rolling.

25. **Phenol** is first mixed with 2 grs. of liquorice for each grain, then triturated vigorously and rolled into pill quickly. A drop of mucilage of acacia may be necessary.

26. **Phosphorus** can be made into pills by the following method:—Phosphorus is dissolved in carbon disulphide and the solution is carefully mixed with oil of theobroma and beeswax, and made into a pill-mass with the addition of a little kaolin. The mass must be kept immersed in cold water in a blue bottle away from light. 3 grs. of the mass and 1 gr. of acacia powder can be rolled into a pill for dispensing.

Pills containing phosphorus require varnishing or a pearl coating.

27. **Potassium Permanganate** requires careful treatment, for it soon oxidises organic matter, such as sugar, syrup, vegetable extracts, etc. when brought in contact with it. It can be made into a good pill-mass by mixing it with kaolin 50 p.c. and then making the pill-mass with lanolin. Work the mass gently. Vigorous rubbing or the introduction of even a trace of foreign matter may set up combustion.

28. **Quinine Sulphate** with tartaric or citric acid makes an excellent mass. Sometimes a drop or two of glycerin or water may be necessary in dry weather. The pills must be varnished or capsuled, otherwise, they will become soft and sticky by damp. Glycerin of tragacanth, is also a good excipient. White excipients should be used for white drugs.

29. **Rhubarb powder** is a troublesome substance for pill-making. Proof spirit or tincture of rhubarb (1 m. to 3 grs.) makes a soft mass which should be rolled quickly. Simple syrup, treacle and equal parts of glycerin and rectified spirit may also be used.

30. Zinc Valerianate makes a good mass with a little powdered acacia and spirit. Glycerin of tragacanth and liquorice powder may answer well.

PILL-COATING

Coating of pills is necessary to make them look more elegant, to disguise their unpleasant taste, to protect them from decomposition by contact with the air, and sometimes to prevent their action in the stomach.

The general rule in the coating of pills is that *all pills requiring a coating should be perfectly made, of a firm consistence, and free from contamination and powder.*

Silvering is done in a covered earthenware pot or a boxwood pill-silverer (Fig. 27). The pills being damped with thin mucilage are dropped on to a silver leaf put within the silverer. The cover is then put on and the silverer is shaken for about a minute. After the superfluous fragments of silver-leaf have been blown off, the pills are exposed to air for a few minutes to dry. One silver leaf covers six 5-gr. pills, and two drops of mucilage are enough to damp a dozen of such pills. When the pills are too damp, more leaf is required for silvering, moreover the finish is not so elegant. A better and finer silvering can be obtained by putting the pills and leaf in a covered porcelain pot or a metallic silverer, heating the pot or silverer over a spirit lamp and rotating it as before.

Pills containing asafetida, mercury and sulphides should not be silvered unless they are very *stiff* and *varnished*, otherwise the silvering will soon get blackened.

Gelatin-coating.—A coating solution is made by dissolving 1 of gelatin in 4 of water on a water-bath, straining while hot, and cooling it afterwards. If there are air bubbles the solution should be repeated. The pills are now stuck on the points of pins or needles and dipped into the warm solution. The pills are taken out slowly and rotated for a few seconds and then stuck into a sheet of cork or pincushion by their opposite ends. As soon as the outside coating dries, the needles are withdrawn, and the holes close of themselves.

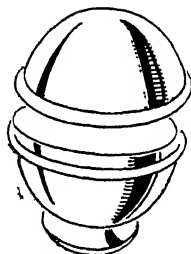


FIG. 27.—Pill Coater or Pill silverer.

or syrup and gum. They are then rotated and gently heated, very finely powdered sugar 7 parts and starch 1 part being dusted on, and the motion kept up till a perfectly dry, hard and whitish coating is obtained, the operation being repeated if necessary.

Pearl coating.—It is done in the same way as sugar coating with the exception that fine white French chalk is used in place of sugar and starch. This coating sometimes becomes too thick so that the gastric secretion fails to penetrate it. For a perfect coating the pills must be dry. If they contain any hygroscopic substances, they should be varnished before coating.

Keratin-coating.—Keratin solution is made by first removing from horn shavings all that is soluble in pepsin and diluted hydrochloric acid, dissolving the residue in alcoholic solution of ammonia or acetic acid, and then evaporating the solution to the consistence of a liquid gum. The pills are simply rotated with this solution in a pot and dried on a slab. The coating often gets sticky. Pepsinised keratin can be bought and dissolved in any of the above solvents. Drugs intended to pass undissolved through the stomach are coated with keratin or salol; as emetine.

Varnishing. The solution used is sandrac 1, alcohol 2, and ether 2. Smear an ointment pot or a porcelain slab with some oil, *e.g.* olive oil or almond oil. Pills for varnishing should be highly polished and free from any powder. Put the varnish in the proportion of 1 drop for each pill in a flat covered pot, cover and rotate for a few seconds say for 15 seconds. Transfer the pills into the oiled porcelain slab or the developing dish and turn each pill over and leave them to dry.

Salol-varnishing. The varnish contains salol 2, shellac 3, absolute alcohol and ether of each 3, which should be applied several times till a thick coating is obtained. Or salol can be melted by heat in a copper bowl and the pills rotated as in sugar-coating.

Enteric-coatings are employed when pills are intended to pass through the stomach unchanged so that they can act in the intestine. The gelatin coated pills are dipped in formaldehyde solution B.P., and dried. Many so-called enteric-coated pills are useless. These coatings are known as "glutoid" coating.

POWDERS

1. **Compound powders.** The B.P. gives no direction as to the manner of mixing compound powders, consequently the dispenser is left to his own experience and resources in compounding them. The following hints, however, will greatly help him.

(a) **Powders must be thoroughly mixed** in a mortar or on paper. Powders mixed by a spatula on paper and sifted are more diffusible in water than those rubbed up in a mortar; but there are exceptions to this rule. Take for example the following prescription:—℞ Sulphur Precip. gr. 20, Guaiac. Res. gr. 10, Magnesia gr. 20. Here the most miscible powder is obtained by triturating guaiacum and magnesia together in a mortar, before adding sulphur, whereas if mixed on paper, it would not diffuse in water. Powders for insufflation should only be loosely mixed on paper.

(b) They should be **passed and repassed through a fine hair sieve** as often as possible. By repeated sifting and shaking in a bottle the ingredients are thoroughly incorporated and a uniformity of colour is obtained.

(c) They should be **very lightly rubbed** in a mortar if this process is at all adopted, otherwise they would cake.

(d) **Ingredients in smaller quantities** should first be thoroughly mixed together, and afterwards large quantities be gradually incorporated.

2. **Folding Paper and Boxes.**—Powders should be folded in ordinary writing paper, or better if possible, in demy glazed powder-paper made for the purpose. Waxed or paraffined paper is to be used for hygroscopic drugs. Coloured paper is used for powders for lotions. Folded powders should be of the same breadth and length, better done on a powder-folder. Powders under six are generally dispensed in a neat small oblong envelope on which the words "The Powder" is printed; but those over six in a cardboard box or bottle with a label gummed outside.

3. **Waxed Paper and Tinfoil.**—Drugs that are perishable, as ergot; that are volatile, as camphor, essential oils; that are hygroscopic, as potassium acetate, carbonate and citrate, sodium iodide, etc.; that are liable to decomposition, as calcium sulphide, valerianates, should be folded first in waxed paper and then each covered with tinfoil and dispensed in a bottle.

4. **Powders in Quantity.**—When a powder is ordered to be given in spoonfuls, it should be dispensed in a well-corked or stoppered, wide-mouthed bottle.

5. **Salts** which mutually decompose each other must be mixed and stirred lightly together in a dry condition; as sodium sulphate with potassium tartrate, potassium nitrate with sodium salicylate.

6. **Oxidising Substances** should be each separately rubbed to powder, and then lightly blended on paper with safe ingredients by a bone spatula.

7. **Hygroscopic Powdered Drugs** should never be kept in paper packets. They should be dried and preserved in wide-mouthed bottles or stone jars with accurately fitted stoppers or corks. Suspending a bag of dry quicklime from the cork helps also to keep powders dry. Powdered squill and ammoniacum can be kept dry in this way.

8. **Division of Powders.**—There should be no guesswork in division. Each one must be weighed.

9. **Liquids** are rarely prescribed in powders, if so, white kieselguhr may be used to absorb them (1 gr. to 1 m.).

CAPSULES AND CACHETS

Capsules are used in place of pills to dispense nauseous and disagreeable drugs. Solids, semi-solids and liquids in small bulk may be dispensed in capsules. They are made of gelatin with varying quantities of glycerin depending upon the hardness required. They are of two varieties, soft and flexible, usually oval in shape for liquid and semi-soft masses; and hard for dispensing powders. They readily become soft, dissolve in the stomach and are taken like pills.

The hard capsules consist of a body and a cap, the latter fitting over the other like a lid. They are filled with a small aluminium funnel, and the powder is pressed through it with a thin glass rod or a stick. The cap or lid is moistened on the inner side with a camel-hair brush and pushed home on the other half to which it adheres.

Soft capsules are oval in shape with a long closed neck. The filling of these capsules requires some practice. The neck is cut off and the measured quantity of liquid is introduced by means of a hypodermic syringe and the open end sealed either by melting the cut end with a hot glass rod or a steel spatula; or by placing on the cut end a little melted glyco-gelatin.

When capsules are intended to act in the intestine without being dissolved in the stomach, they should be coated with a solution of



FIG. 28.—Cachets showing “dry seal” (*a* and *b*), and “wet seal” (*c* and *d*) open and closed.

keratin or immersed in a solution of formaldehyde, B.P. for ten minutes. They are then known as enteric coated or ‘glutoid’ capsules.

Cachet forms an excellent medium of prescribing nauseous and bitter powders, of larger amount than can be given in a capsule. They are made of wafer paper so that they become soft and pulpy when moistened with water and these can be easily swallowed without tasting the drug. They are made of two kinds, one ‘wet seal’ and the other ‘dry seal’.

The dry closing cachets consist of two halves one fitting over the other like hard gelatin capsules. These are very easy to fill. The required quantity of the drug is placed in one half and the other half or the lid is placed on it.

The wet seal cachets consist of two halves with a broad rim. The powder is deposited in one half, the margin of the other half is moistened with water and placed over the other and the rims pressed together. These are best filled by wet-closing cachet machine.

The machine consists of three plates joined by hinges (fig. 29). The plates have two or more sets of holes so that different sizes of

cachets may be used in the same machine. The plates being open, one half of the cachet is placed in the hole in plate A and the other half into the corresponding hole in plate C. The plate A is now covered with plate B and the empty cachets are filled with the required quantity of powder through the funnel D with the help of

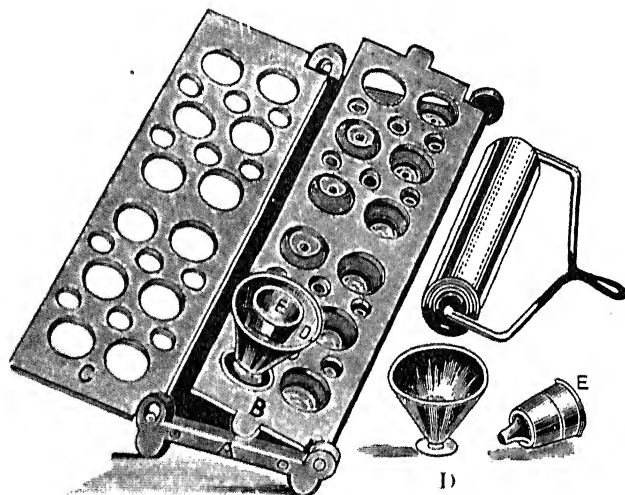


FIG. 29.—Cachet Machine.

thimble E. The middle plate is now removed and the rims of the empty cachets on plate C are damped with the roller moistened with water and the plate turned over and lightly pressed on plate A so that two halves of the cachets get fixed. The finished cachets are then gently removed and served in boxes.

BLISTERS

1. **Blister Spreading.**—A blister is best spread over an adhesive plaster, which has been previously spread upon glazed thin calico. First of all the dispenser should cut a “shape” an exact size and form of the blister ordered—out of a square piece of writing or packing paper, leaving all round a margin 1 inch wide. This is best done by folding the square piece twice upon itself, and cutting by a pair of scissors the shape of the blister out of the middle, rejecting the cut out central piece. This *empty space is the shape of the blister*. The dispenser now cuts a piece of spread adhesive plaster or adhesive plaster mull one inch bigger than the size ordered, and gently warms it to make it slightly sticky, and quickly lays the “shape” upon its sticky surface, and evenly presses it down (in India the warming of the adhesive plaster is not often necessary during hot months). He then takes a quantity of the B.P. cantharidin plaster sufficient for the size and softens it well between his thumb and fingers. Taking a small pellet, he spreads over the adhesive surface, with the side and front of his right thumb, while the fingers of his left hand keeps the plaster *in situ*. He goes on making a series of rainbow-like strokes from left to right till the whole of the surface within the shape is covered. A long spatula, not unlike a large dinner knife, is gently warmed, and firmly passed over the spread cantharidin, removing any superfluous plaster and making its surface smooth. The paper shape is now removed, and the edges are neatly trimmed, keeping a

margin of the plaster three-eighths of an inch wide. A piece of oiled or waxed paper is now loosely laid over the blister and the whole put within a paper box.

2. Powdered Cantharidis, Blistering Liquid or Olive Oil should not be sprinkled or applied to increase the action, or improve the appearance, of the blister.

3. Paper-Covering should be removed before use, otherwise the blister will not stick. Both the dispenser and prescriber should give directions to this effect. A better plan is to pin the margins to a piece of paper which is then stuck to the bottom of the box.

PLASTERS

Most of the plaster-mulls of the market are made by machinery. Dispensing of such a spread plaster means the cutting of a piece ordered. It is only when a special plaster is ordered that the dispenser is required to make one on the counter. The spreading of a plaster requires great skill and dexterity.

1. **Plaster spreading.**—A plaster is made in the same manner as a blister, except that the method of spreading is different. Sheepskin, stiff chamois, dymity, moleskin or sometimes adhesive plaster-mull is used, but the white sheepskin is generally preferred when not otherwise ordered by the prescriber. The "shape" is cut in the same way as for a blister. A piece of leather larger than the size of the plaster ordered, is cut off and stretched out in all directions by pulling. The leather is now placed with its rough surface upwards on a thick pad of paper, and the gently warmed plaster iron is passed over it to remove any wrinkles or inequalities. The paper shape merely dipped in water is evenly pressed against this rough surface, and all the necessary appliances being in readiness the process of spreading is begun in one or other of the following ways:—

(a) The plaster is cut into thin slices, put in a small enamelled pan with a lip and handle, and warmed over a gas flame or fire, stirring it constantly and not allowing it to boil. In the meantime the leather, the shape, and the plaster iron or spatula are kept ready as already described. As soon as the plaster becomes creamy, it is poured over the leather within the shape at the left end, then with a long spatula or a plaster iron it is spread rapidly over the surface, any superfluous plaster being removed and returned to the pot.

(b) The easiest and most convenient method of spreading is to cut a piece of plaster from the stick, allowing 15 grs. for each square inch of plaster required, and to put it on a sheet of strong, smooth, brown paper. Having prepared the shape and the leather, melt the cut-off piece to a creamy consistence by gently rubbing a hot plaster iron over it, and scrape the mass to the edge of the paper. The leather with the shape, having been brought alongside with one or two sweeps the dispenser covers the whole surface, removing any superfluous plaster with a spatula. A second hot iron may be required at this stage.

A mixture of plasters can be made by a similar process.

2. **Plaster with an adhesive margin** is made in the following manner:—The shape is cut as before, and the central piece instead of being thrown away, is damped and stuck to the middle of the leather. The shape is again folded up, and a piece of the width of the intended adhesive margin is cut off; and the shape is pressed against the leather, thus leaving a free space between the centre-piece and the shape; which space is now covered over with the adhesive plaster. When cold, remove both the papers and apply a second shape cut to the proper size, having previously coated it lightly with soft soap to prevent it from sticking to the adhesive margin. The plaster is now spread in the ordinary way, the shape

removed, and any soap that may have adhered to the margin is wiped away with a wet cloth or sponge.

The Writer's Method. The plaster is spread as usual and the shape is pulled off, and the margin of the leather trimmed, leaving exactly the width to be covered over with the adhesive plaster. The dispenser now melts a small piece of adhesive plaster in a gallipot, and with a spatula spreads it over the margin and finally smooths it by passing a hot spatula over.

3. Plasters for bed-sores are spread on chamois leather without margins.

4. Mammary plasters must be circular in shape, 7-in. in diameter, with an opening 2-in. in diameter in the centre. The margin is to be notched to fit these plasters to the curved surface of the breasts.

SUPPOSITORIES, PESSARIES AND BOUGIES

1. **Basis.** Oil of theobroma is the official basis. It should be liquefied on a water-bath in a casserole or a porcelain evaporating dish. In India and the Colonies, where the prevailing temperatures are higher than in England, a sufficiency of white beeswax may be added to raise the melting-point to the necessary degree. An alternative method is to use *glyco-gelatin basis*, which consists of gelatin 25; glycerin 40 (by wt.); and water 80 (by wt.). This should only be used when ordered, since gelatin is incompatible with several substances including tannin.

2. **Ingredients** should be treated like those for ointments. Any powder or crystalline substance must be rubbed very fine with a little cacao butter, before mixing with the melted oil of theobroma.

3. **Moulds** are necessary to make suppositories. They are made of heavy gun-metal with six to twelve holes into which the melted suppository mass is poured. The mould is divided longitudinally so that it can be opened and cleaned. Each half of the mould contains the corresponding hollows, which when fixed and screwed form the entire suppository holes. They are so made that each hole has the capacity of holding 15 gr. or 30 gr. suppository.

Moulds must be perfectly clean and cooled with ice or cold water and the inner surface of the hollows lubricated with a piece of cotton wool soaked in soap liniment and glycerin, equal parts, or with soap liniment 3 parts and almond oil 1 part. Almond oil is necessary for gelatin suppositories.

4. **Operation.** Triturate as in para 2, and mix with the melted oil of theobroma with constant stirring, until a creamy mass without lumps is obtained, and then pour it into the moulds, or divide into equal parts when hard, and mould them with the fingers into the shapes of suppositories, pessaries and bougies. Finely powdered starch prevents them from sticking during manipulation.

5. **Capacity and Displacement.** Ordinarily a mould will hold 15 gr. of oil of theobroma, but may hold more or less, depending on the density of the drug used. The quantity of the medicament which will displace one part of cocoa butter is known as the *displacement value*. This requires to be taken into consideration when calculating the amount of oil of theobroma necessary for each suppository. Thus 0.9 gr. of tannic acid and 3.6 gr. of iodoform will displace 1 gr. of oil of theobroma.

SUPPOSITORIES AND BOUGIES OF SPECIAL DRUGS

1. **Adrenaline** should be dissolved in about 10 minims of 1 in 30 boric acid solution and then mixed with suppository basis which consists of a mixture of oil of theobroma and sodium stearate $\frac{1}{2}$ gr. for each suppository ordered. Stir till an emulsion is formed and pour into the mould when about to set.

2. **Alkaloids.** -Alkaloidal salts are generally better absorbed than

pure alkaloids, and therefore the salts instead of the alkaloids should be used dissolved in oleic acid.

3. Boric Acid makes a good mass if glycerinum acidi borici and gelatin basis are mixed together.

4. Chloral Hydrate should not be mixed with heated cacao butter, but rubbed up with cold cacao butter and a little wax, if necessary, and pressed into the mould.

5. Extracts must be made into a smooth paste with water or proof spirit, and gradually mixed with the melted basis.

6. Ichthammol suppositories are made with glyco-gelatin basis when each suppository is more than 2 grs., otherwise oil of theobroma may be used. The ichthammol should be added directly to the melted oil of theobroma.

7. Iodoform makes good bougies and suppositories with cacao butter by the cold process. The crystals must be finely powdered in a glass mortar before being incorporated in the oil.

Despatching.—These preparations should be sent out wrapped in absorbent cotton-wool. In hot weather, they may be dispensed in a wide-mouthed stoppered bottle containing iced water. If they contain volatile ingredients, each of them should be covered with waxed paper or tinfoil.

TINCTURES

In the preparation of tinctures three things are essential, *viz.*—(1) the Solvent; (2) the Process; and (3) the Ingredients.

1. **Solvent.**—Alcohol of various strengths is used in the preparation of most tinctures. One only, *viz.* Tinct. Lobelæ Ætherea is prepared with ether. Ammonia is used in the preparation of tinct. valerianæ ammoniata. Glycerin and distilled water are used to help solution of active ingredients.

2. **Process.**—Any of the following processes is used for making tinctures—

(a) **Maceration.**—Place the solid materials with the whole of the menstruum in a closed vessel, shake occasionally during seven days; strain; press the marc, mix the strained and expressed fluids, filter. It takes seven days and is not economical.

(b) **Percolation.**—Moisten the solid materials with sufficient menstruum, set aside for 4 hours in a well-closed vessel, pack in a percolator, add sufficient menstruum to saturate the material. When the liquid drips from the percolator close the outlet, add sufficient menstruum to leave a layer above the drug. Macerate for 24 hours. Allow to proceed till the percolate measures about three-fourth of the volume required for the finished tincture. Press the marc, mix the expressed liquid with the percolate, add sufficient menstruum to produce the required volume, filter.

(c) **Simple Solution.**—This method is adopted when tinctures are made by dilution of a liquid extract or a stronger tincture.

3. **Ingredients.**—These require to be carefully selected. Most of them are to be powdered according to the degree of comminution as prescribed by the B.P. Some are to be cut small, some to be bruised and some are used in their natural state.

LOZENGES

1. The B.P. lozenges are made like a pill-mass (*see* page 34).

2. **Ingredients.**—The essential ingredients for making lozenges are finely powdered or icing sugar, mucilage of picked gum acacia, and medicinal and flavouring agents.

3. **Operation.**—The ingredients having been thoroughly mixed and kneaded, the resulting paste is placed on a slab with adjustable edges and rolled out to the desired thickness. The lozenges are then cut out with a punch and exposed to the air for 12 or 24 hours, after which they are removed to a drying chamber.

4. **Stamping.**—While the lozenges are still soft, they are stamped with letters indicative of their composition.

5. **Packing.**—Lozenges should be kept in dry, well-fitted stoppered bottles in a dry place. Dampness makes them sticky. They are to be dispensed in wide-mouthed stoppered bottles.

OINTMENTS

1. The preparation of ointments is not always easy. Special tact and care can only turn out a good product. The following general hints are worth remembering:

(a) If the active drug is a *solid* or a *powder*, as galls, mercuric iodide, sulphur, etc., it should be reduced to a state of fine powder before admixture with the basis, so that the ointment may be free from grittiness.

(b) If it is a *soluble* or *deliquescent salt*, as potassium carbonate or iodide, it should be first made into a thin paste with water before mixing with the basis.

(c) If it is a *hard extract*, a *balsam*, or a *resin*, a preliminary treatment is necessary with such substances as water, oil, glycerin, or rectified spirit, as the case may be.

(d) If it is a *liquid extract*, as in the case of belladonna ointment, it must be evaporated to the required consistence.

(e) If it is an *alkaloid*, as aconitine, atropine or cocaine, it should be dissolved in oleic acid by trituration and gentle heat.

(f) If it is a *crystallised drug*, as boric acid, salicylic acid, iodoform, etc., it should be reduced to a fine powder, and triturated with its own weight of the basis for a while before adding the rest. Tannic acid should first be dissolved in glycerin.

(g) If it is a *volatile substance*, such as menthol, chloral hydrate, hydrocyanic acid dilute, it should be mixed after all the ingredients have been incorporated so as to reduce its evaporation to a minimum.

2. **Basis.**—Ointment bases are of two kinds, (1) *those used when the active ingredients are intended for absorption from the skin*, and (2) *those used when the medicaments are intended for local action only*. For the former class of ointment lard, or benzoinated lard or suet or benzoimated suet are used. For the latter class soft or hard paraffin or both with or without beeswax are used. In both cases wool fat may be added if a large quantity of liquid is to be incorporated.

Whatever basis is selected it should not be a chemical incompatible, nor should it in any way affect the action of the ointment. Rancid lard or ointment should not be used. If the basis becomes too soft on account of the prevailing high temperatures, as in India and the Colonies, benzoinated lard, lard, suet, or beeswax may be added as required.

When the basis contains substances like hard paraffin, beeswax, lead plaster or such ingredients which are solid at the ordinary temperature, and have to be incorporated with soft paraffin, lard, suet or an oily substance, it is necessary that they should be prepared by fusion, *i.e.* by melting them in a porcelain dish on a water bath. The substances with a high melting point should be shredded and melted first and the other ingredients of the base added according to their melting point.

3. **Incorporation of a liquid** with a fatty or oily basis is best effected by slowly adding the liquid drop by drop, and keeping up a steady rotatory motion. The mortar must be warmed beforehand.

4. **Spatulas.** A bone or boxwood spatula is the best for scraping, stirring or mixing ointments.

5. **Two ointments**, or an ointment and a liquid or oily substance, are best mixed on a porcelain slab.

6. **Oleates** should not be melted in a metallic cup, but in a porcelain casserole.

7. **Tinctures and spirituous substances** are best incorporated with a fatty medium by spreading the latter evenly on the bottom and side of a mortar, and mixing the tinctures gradually.

Despatching.—Ointments should be sent out in earthenware pots with celluloid caps, a piece of waxed paper intervening between the cover and the ointment. They may also be sent out in glass jars having glass or aluminium covers. Collapsible tubes are convenient for small quantities and when the ointment is made by fusion. When open pots are used a tinfoil should be used over the waxed paper.

OINTMENTS OF SPECIAL DRUGS

1. **Unguentum Phenolis, B.P.** is best prepared by using liquefied phenol and a cold basis, as a previously prepared part of the phenol crystallises on keeping. This is obviated by dissolving the phenol in glycerin

2. **Chrysarobinum, B.P.** when dissolved by heat partly recrystallises on cooling, as happens in the B.P. ointment. It being more soluble in castor oil than lard, a mixture of the two gives satisfactory results.

3. **Glycerin** can be well incorporated with extracts by first rubbing the extract with a little hot water in a warm mortar and then adding glycerin gradually.

4. **Hydrargyri Perchloridum** is sometimes prescribed in the shape of ointment. It must be well triturated with glycerin (2 ms. to 1 gr.) before mixing with basis, otherwise minute particles of it may violently irritate the skin. When ordered with potassium iodide, each should be triturated first before admixture

5. **Iodide.**—First triturate, then add a few drops of rectified spirit and rub with its own weight of fatty basis, and lastly mix with the remaining basis.

6. **Paraffin ointment, B.P.**—Unless the melted paraffins are stirred well, the ointment is sure to be lumpy. White soft paraffin should be used for colourless ointments.

7. **Resorcin** readily absorbs oxygen and becomes discoloured.

8. **Thymol crystals** are very irritating to the skin. With camphor (1 in 1), thymol forms a liquid which can be worked up into an ointment.

9. **Eye ointments or oculenta** must be prepared under aseptic conditions according to the directions given in the B.P. Suitable glass rods for the application of the ointment should be supplied and their use explained to the patient.

STERILISATION

The use of different preparations which are introduced into the body through different channels and of other preparations like the ointments for the eye, demands that these should be sterile, *i.e.* free from living micro-organisms. A knowledge of the various methods of sterilisation is therefore necessary. The methods generally adopted for the purpose involve either application of heat (moist or dry), filtration, use of certain chemicals, or a combination of these. Whatever method may be adopted it must be such as will not inactivate the medicament, or render the preparation subjected to the process, unsuitable for the purpose for which it is specially intended.

Since heat kills most bacteria, sterilisation by heat is generally the most suitable and convenient method. It is therefore the method of choice for thermostable substances, while filtration is adopted for thermolabile substances. Certain chemicals have a marked disinfectant action and kill most bacteria. Their relative value has already been discussed (*see* page 546), but it is necessary to mention that some of these substances are used as a preservative in sterile solution as a precaution against possible reinfection. The chemicals generally used are phenol, cresol and chlorbutol. Sodium chloride increases the potency of phenol and cresol as antiseptic.

The Pharmacopœia sanctions the following methods for sterilisation:

1. *Heating in an Autoclave.* Glass vessels and containers, and various solutions or suspensions for injection should be sterilised in an autoclave. Glass containers require a heating for one hour at 150°C. When the volume of each container does not exceed 100 mls, the containers are exposed to steam at 115° to 116° for thirty minutes, and this temperature is reached when the pressure of the steam is 10 lbs. per square inch above the atmospheric pressure. When the containers contain more than 100 mls of fluid, they are exposed for a longer period, sufficient to ensure that the whole of the solution in each container is maintained at the temperature of 115° to 116° for thirty minutes.

2. *Tyndallisation.* By this is meant intermittent heating at temperatures between 60° to 80° for three successive days for materials which are not immediately wanted for use and which will not be injured by a temperature of 80°. The principle underlying this method is that most bacteria are killed during the first heating but not the spores, so they are exposed for three successive days to allow the spores to germinate and thus make them susceptible to the action of subsequent heat.

3. *Filtration.* This consists in passing the material to be sterilised through sterile bacteria-proof filter (Berkefeld or Chamberland). The filter should be first sterilised by heating in an autoclave at 115° to 116° for thirty minutes, or in a steam steriliser for one hour on three successive days. All substances sterilised by this process must comply with sterility tests prescribed by the B.P. before being used. This method is applied to those substances which would be inactivated by heat.

4. *Emergency Method.* The solution is first prepared by aseptic methods and an antiseptic is added in such concentration as will prevent the growth of bacteria at least as effectively as 0.5 p.c. *phenol*. The solution is distributed into previously sterilised containers and sealed. These are heated by immersion in water or by other means so as to maintain the temperature of the solution at 80° for not less than 30 minutes. The containers are labelled giving the date and the warning "keep in a cool place and use within four days." In solutions intended for intravenous injection the addition of the antiseptic is omitted; and the solution is prepared by aseptic methods, and then boiled for fifteen minutes.

5. *Sterilisation of Oily Solutions.* These should be sterilised by heating to 150° for one hour. When this cannot be done without producing physical or chemical change, the solution or suspension is prepared by aseptic methods, and oil, which has been heated to 150° for one hour is used. This is then transferred to previously sterilised containers and these are sealed to exclude bacteria.

APPENDIX I

EXTRACT FROM THE RULES FOR REGULATING THE POSSESSION FOR SALE AND THE SALE OF POISONS

Under Indian Poisons Act, 1919 (xii of 1919)

* * * *

15. The following restrictions shall apply to "whole-sale" of poisons:

(a) All receptacles containing poisons shall be securely packed and bear the label "Poison," the name of the poison, and, at the time of sale, the name and address of the seller as well, except where the manufacturer's name appears thereon.

(b) In case of sale of poisons included in Schedule I, a stock and sale register in the form appended to these rules, shall be maintained in which all transactions shall be entered from day to day in the manner indicated therein, provided that no signatures of purchasers shall be necessary and sales may be posted in lots of all poisons sold under a particular order according to the serial numbers of the transactions. All letters or written orders referred to in the fifth column of sale registers shall be preserved in original, where possible, for 2 years from the date of sale.

16. The following restrictions shall apply to "retail sale" of poisons included in Schedule I:—

(a) Every vessel, package or covering containing poisons shall be labelled with the name of the poison, and the word "Poison" and in case of preparations for external use only the words "not to be taken" in addition, distinctly printed both in English and vernacular, in red letters.

Note.—In exceptional cases when printed labels are not immediately available, written labels may be used. If labels are written, only block capitals and red ink shall be used.

(b) All poisons which are kept for sale by the licence-holder under these rules shall be kept in a box, almirah, room or building (according to the quantity maintained) secured by lock and key, and in which no substance shall be kept other than poison possessed in accordance with a licence granted under the Act, and each of these poisons shall be kept in a separate closed receptacle within such box, almirah, room or building. Every such box, almirah, room or building and every such receptacle shall be marked with the word "Poison," in red characters both in English and vernacular and in the case of receptacles kept for separate poisons, with names of such poisons.

(c) When any poison is sold it shall be securely packed in a closed receptacle or packet which shall be labelled by the vendor with a red label bearing the name of the poison and the word "Poison" and in case of preparations for external use only, the words "not to be taken" in addition, in English and vernacular, and the name and address of the vendor, together with the date of sale.

(d) Every sale of such poisons shall, so far as possible, be conducted by the licence-holder in person or where the licence-holder is a firm or company, through or under the supervision of an accredited representative of such firm or company or, in either case, through a qualified compounder.

(e) A licence-holder shall not sell any poison to any person unless he is personally known to him, or is identified to his satisfaction or,

to any one who is apparently under 18 years of age, or to any one who does not appear to him to be in full possession of his faculties, or to any wandering mendicant.

(f) Every licence-holder shall maintain a stock register in the form appended to these rules in which he shall enter or cause to be entered the sales of poisons specified in Schedule I according to the instructions contained in the register. Separate pages shall be allotted in the register for each particular poison and the licence-holder shall enter or cause to be entered thereon, side by side, all stock and sales of poison. The register shall be totalled and balanced daily and the licensee shall be himself responsible for its correctness.

(g) The licensee shall completely fill in the prescribed sale register before delivery of such poisons.

(h) A licence-holder shall not sell powdered white arsenic unless the same is, before the sale thereof, mixed with soot, indigo, or Prussian blue in the proportion of at least $\frac{1}{2}$ oz. soot, indigo or Prussian blue to 1 lb. of white arsenic and so on in proportion for any greater or less quantity; provided that where the licensing authority is satisfied that such arsenic is required for some purpose for which such admixture would, according to the representation of the vendor render it unfit, the said licensing authority may authorise the vendor in writing to sell without such admixture such quantity of white arsenic as the licensing authority may think proper.

17. The following restrictions shall apply to the "sale of poisons" included in Schedule I "by dispensing of prescriptions":—

(a) The stock of poisons for dispensing purposes shall be kept in the dispensing room in a separate almirah or shelf and the room or the almirah shall be locked up after dispensing hours. Such poisons shall be kept in separate bottles or other receptacles distinguishable by touch and colour from ordinary bottles and receptacles and marked with the word "Poison" in English and the vernacular and the name of the poison in red letters in English.

(b) When a poison is sold without any mixture, all restrictions referred to in rule 16 (c), (d), and (e) regarding poisons sold and method of sale, shall apply.

(c) A stock register in the form appended to these rules shall be maintained and kept up to date, but the consumption of poisons in the dispensing room need not be shown on the sale side of the register but a record of the prescriptions under which poisons are sold shall be preserved for 2 years.

18. Where the sale of poisons included in Schedule I is carried on both by retail and by prescriptions, poisons issued from stock to the dispensary on any day, shall be entered forthwith as one item on the issue side of the register with a note to that effect, provided that the stock so transferred shall not exceed a reasonable quantity. No detailed particulars are, however, required to be maintained in the said register regarding the consumption of such poisons in the dispensary for dispensing purposes.

19. All the restrictions mentioned in rule 16 (a), (b), (c), (d) and (e) shall apply to the possession for sale and sale of poisons enumerated in Schedule II.

SCHEDULE OF POISONS

SCHEDULE I

1. Aconite, Aconitine, Lin. Aconite, Tinct. Aconite.
2. Arsenic metal, Arsenious Oxide (white arsenic), Yellow Arsenic (arsenic sulphite, yellow orpiment), Red Arsenic (Realgar), Copper Arsenite (Scheele's green), Copper aceto-arsenite (Paris green), Liq. Arsenicalis, Liq. Arsenic Hydrochloride, Arsenic chloride, Arsenic bromide
3. Atropine, Atropine Sulphate, Liq. Atropin. Sulphate, and other salts and preparations of atropine.

- 4 Barium Sulphide.
5. Belladonna root, Belladonna leaves, Extracts and Liquid Extracts of Belladonna, Liniment Belladonna
6. Cannabis Indica, Extract of Cannabis Indica
- 7 Cocaine, Cocaine Hydrochloride, and other salts and derivatives of Cocaine, both synthetic and natural, except such as are exempted under the Excise Act.
- 8 Corrosive Sublimate (Mercuric Chloride).
- 9 Cyanide of Potassium, Cyanide of Sodium, Acid Hydrocyanic (prussic) concentrated and dilute.
- 10 Datura Folio, Datura Seeds (Stramonium)
11. Morphine, Morphine Hydrochloride, Liq Morphine Hydrochloride, Morphine Acetate, Liq Morphine Acetate, Heroin, Heroin Hydrochloride, and other salts and derivatives of morphine
12. Nux Vomica Seeds, Extract of Nux Vomica Solid, Liquid Extract of Nux Vomica, Tinct of Nux Vomica
13. Opium, Tinct. of Opium, Extract of Opium solid, Extract of Opium Liquid, Liq. Opii Sedativus.
14. Phosphorus yellow
15. Picrotoxin
- 16 Savin oil (oil sabinæ)
17. Strychnine, Strychnine Nitrate, Strychnine Sulphate, Strychnine Hydrochloride, Liq Strychnine Hydrochloride, and all other salts and solutions and preparations containing 0.2 per cent. or more of strychnine.
18. Tetra ethyl lead.

SCHEDULE II

1. Antimony compounds, both organic and inorganic
- 2 All organic compounds of Arsenic, and all other inorganic compounds of Arsenic except those mentioned in Schedule I
3. Barium Nitrate, Barium Chloride.
4. Cantharides, Tinct Cantharides, Cantharidin, Tinct Cantharidin.
5. Carbolic acid containing not less than 3 per cent. of phenol.
- 6 Chloral hydrate
- 7 Digitalis Folio, Tinct Digitalis, Digitalin.
8. Hyoscyamus (Henbane or Khoiasani Ajwan) leaves, Ext Hyoscyamus Liquid, Tinct. Hyoscyamus, Liq. Hyoscyamine Sulphate, Hyoscyamine Hydrobrom.
9. Mercury oxides (red, yellow or black), Ammoniated Mercury, Mercury Sulphocyanide, Mercury Iodide, Liq Hydrarg. Perchlor.
10. Nitric Acid, concentrated.
11. Oxalic acid, Sodium Oxalate, Potassium Oxalate, Ammonium Oxalate
12. Red Phosphorus, Rat poison containing red phosphorus.
13. Strophanthus, Strophanthin, Ext Strophanthus Liq, Tinct. Strophanthus.
14. Tinct Belladonna.
15. Chloroform.

Stock Register

NAME OF THE FIRM.....

ADDRESS.....

NAME OF THE POISON

Date of receipt.	Name and address of person or firm from whom received.	Quantity received.	Date of sale.	Amount sold.	Balance in stock

Sale Register

NAME OF THE FIRM.....

ADDRESS.....

NAME OF THE POISON

Date of sale.	Name and address of purchaser.	Purpose for which wanted.	Quantity sold.	Signature of purchaser (or thumb-impression if illiterate) or in case of purchase by post, date of letter or written order and reference to the original in the file in which it is preserved.	Remarks.

APPENDIX II

CONTRACTION OF WORDS AND PHRASES USED IN PRESCRIPTIONS

The following contractions of words are ordinarily used in prescriptions .—

<i>Contr.</i>	<i>Name</i>	<i>Meaning</i>	<i>Contr.</i>	<i>Name</i>	<i>Meaning</i>
aa	Ana	Of each	M.	Misce	Mix
Ad	Adde	Add	M. or Min.	Minimum	A Minim
Amplus	.	Large	Mag	Magnus	Large
Aq.	Aqua	Water	Mane	...	In the morning
Aut		Or			
C	Cum	With	Mist.	Mistura	A mixture
Cap, Cpt.	Capiat	Let the patient take	Mitte	.	Send
			Mol	Mollis	Soft
Cibus	..	Food	Nox	..	Night
Colo	.	To strain	Om.	Omnis	All, every
Co. or Comp.	Compositus	Compound	Post	...	After
Cras		To-morrow	R	Recipe	Take
Cum	..	With	Rept.	Repetatur	Let it be repeated
Cyath.	Cyathus	A glass			
Div.	Divide	Divide	Sig	Signa	Mark thou
Et	..	And	Sine	..	Without
F.	Fac	Make	Ss.	Semis	Half
Ft	Fiat	Let it be made	Somnus		Sleep
Garg.	Gargalisma	A gaigle	Stat.	Statim	Immediately
Gr	Granum	A grain	Sum.	Sume	Take
Gtt.	Gutta	A drop	Talis	..	Such
Haust.	Haustus	A draught	Una	..	Together
H	Hora	An hour	Vel	..	Or
In		In or into	Ver.	Verus	Genuine
Ind.	Indies	Daily	Vesp	Vesper	The evening
Levis		Light	Vetus	..	Old
M.	Massa	A mass	Vitellus		The yolk of an egg.

The following contractions of phrases are often used in prescriptions :—

<i>Contraction</i>	<i>Phrase</i>	<i>Meaning</i>
Ad lib	Ad libitum	At pleasure.
A. H.	Alternis Horis	Every other hour.
A. C.	Ante cibum	Before food
Aq Bull.	Aqua Bulliens	Boiling water.
" Dest.	" Destillata	Distilled water.
" Ferv.	" Fervens	Hot water.
" Font.	" Fontalis	Spring water.
" Pluv.	" Pluvialis	Rain water.
Bis ind or B.D.	Bis indies	Twice daily.
B P. or Ph. B.	Pharmacopœia Britannica	British Pharmacopœia
C.M.	Cras mane	To-morrow morning.
C N	Cras nocte	To-morrow night.
Coch. amp.	Cochleare amplum	A table-spoonful.
" mag.	" magnum	Do.
" mod.	" modicum	A dessert-spoonful.

Coch. min	...	Cochleare minimum	...	A small spoonful or a teaspoonful
" parv.	" parvum	...	A tea-spoonful
C Vinar.	...	Cyathus Vinarius	...	A wine-glass.
Dieb. alt.	...	Diebus alternis	...	On alternate days.
D. in p. æ or {	...	Dividatur in partes {	...	Let it be divided into
Div. in p. æq {	...	" æquales }	...	equal parts.
F. A. O.	...	Folio Argenti Obduantur	...	Let it be rolled in silver leaf.
Ft. Haust.	...	Fiat Haustus	...	Let a draught be made
F. M. or Ft. Mist	...	Fiat Mistura	...	Let a mixture be made
Ft. Mass in {	...	Fiat Massa in pilulis {	...	Let a pill mass be made
pill. xii div. {	...	" xii divide }	...	and divide into 12 pills.
H. D.	Hora decubitus	...	At bedtime
H. S. or H. S. S.	...	Hora Somni Sumendum	...	To be taken at bedtime.
M. B	...	Misce Bene	...	Mix well.
M. D. U.	...	More dicto utendum.	...	To be used as directed.
M. P	...	Massa Pilularis	...	A pill mass.
Mic. pan.	...	Micra panis	...	Crumb of bread.
O H.	...	Omni Hora	...	Every hour.
O. M.	...	Omni mane	...	Every morning
Omn. bih	...	Omni bihora	...	Every two hours.
O N.	...	Omni nocta	...	Every night.
P. C	...	Post Cibum	...	After food.
P. P. A.	...	Phiala prius agitata	...	The bottle to be first shaken.
P. R. N.	...	Pro re nata	...	When required, occa- sionally.
Q S.	...	Quantum sufficiat	...	Sufficient quantity.
Q. H.	...	Quaque hora	...	Each hour.
S. O. S.	...	Si opus sit	...	If necessary.
S S.	...	Statim sumendum	...	Immediately to be taken.
T d.	...	Ter in die	...	Thrice daily.

APPENDIX III

ALTERNATIVE PREPARATIONS SANCTIONED FOR USE IN TROPICAL, SUBTROPICAL, AND OTHER PARTS OF THE BRITISH EMPIRE

Aurantii Cortex.—In parts of the Empire where bitter oranges cannot be obtained, either dried bitter-orange peel or fresh sweet orange peel may be used in preparing tincture of orange.

Emplastra.—Varying quantities of hard soap, colophony, or yellow beeswax, may be employed in the preparation of the plasters of the Pharmacopœia, when prevailing high temperatures otherwise render the basis too soft for convenient use; but the official proportion of the active ingredient must in all cases be maintained.

Extracta Liquida.—Any Pharmacopœial liquid extract containing less than 30 p.c. v/v of ethyl alcohol, may have the proportion increased to an amount not exceeding 30 p.c. v/v of the extract, where otherwise the preparation would be liable to ferment.

Limonis Cortex Siccatus.—When fresh lemon peel cannot be obtained, dried lemon peel may be used in preparing fresh and concentrated compound infusions of gentain, syrup of lemon, and tincture of lemon.

Oleum Olivæ.—In parts of the Empire where olive oil is not readily available, arachis oil or sesame oil, but no other oil or fat, may be employed in place of olive oil in making the official liniments, plasters, ointments, and soaps for which it is directed to be used.

Unguenta.—Varying quantities of benzoinated lard, lard, suet, yellow beeswax, or white beeswax, may be employed in the preparation of the ointments of the Pharmacopœia when prevailing high temperatures otherwise render the basis too soft for convenient use; but the official proportion of the active ingredient must in all cases be maintained.

INDEX

A

A. B. C. Linnæus, 282
 Abietis Oleum, 523
 Abrodil, 403
 Absolute Alcohol, 141
 Abstracts, 20
 Acacia, 655
 Acacia Gumm, 655
 Accessory Therapeutics, 2
 Accommodation, Action on, 224
 Accumulation, 51
 A. C. E. Mixture, 162
 Aceta, 15
 Acetanilidum, 427
 Acetarsol, Acetarsone, 493, 512
 Acetanum, 367
 Acetone, 572
 Acetopyrin, 427
 Acetphenetidin, 426
 Acetyl Bromo salicylic Acid, 432
 Choline, 222, 233
 Iodo salicylic acid, 432
 methyl salicylate, 432
 para amino salol, 432
 Salicylic Acid, 431
 Acid Margosa, 710
 Potassium Lactate, 313
 Prussic dil., 336
 Quinine Hydrochlor., 441
 Sodium Phosphate, 344
 Acidosis, 626
 Acids, 4
 diluted, 15
 Acidum Aceticum, 108
 Dilutum, 108
 Glaciale, 108
 Acetyl salicylicum, 431
 Acetylannum, 367
 Arseniosum, 486
 Ascorbicum, 587
 Benzoicum, 438
 Boricum, 572
 Caeodilicum, 494
 Camphoricum, 541
 Carboicum, 558
 Chromicum, 136
 Citricum, 109
 Cresylicum, 562
 Hydrobromicum Dil., 209
 Hydrochloricum, 110
 Dil., 111
 Hydrocyanicum Dil., 336
 Hypophosphorosum Dil., 112
 Lacticum, 115

Acidum Mandelicum, 399
 Nitricum, 111
 Dil., 111
 Nitro-hydrochloricum Dil., 111
 Oleum, 660
 Phosphoricum, 112
 Dil., 112
 Salicylicum, 431
 Sulphuricum, 112
 Aromat., 113
 Dil., 112
 Tannicum, 367
 Tartaricum, 110
 Trichloroaceticum, 109
 Trichlorophenicum, 559
 Aconine, 283
 Aconitum, 281
 Acquired Immunity, 664
 Acridflavine, 567
 Act, Indian Poisons, 734
 Action, direct, 61
 Local, 61
 Primary, 61
 Remote, 61
 Secondary, 61
 Action of drugs, the 61
 chemical composition and, 62
 ionisation and, 63
 factors modifying, 47
 reaction of body fluids and, 65
 Active Immunity, 665
 Adalin, 201
 Adeps, 15, 660
 Benzoinatus, 660
 Lance, 660
 Hydrosus, 660
 Adepsin Oil, 658
 Adhatoda, 701
 Adhesive Plaster, 524
 Administration of Drugs, 43
 time of, 51
 Adnephrine, 287
 Adrenaline, 287
 Inhalant, 287
 Suppositories, 287
 Adrenergic, 222
 Adsorbate of Vitamin B₁, 584
 Adsorbents, 339
 Adulteration, 7
 Ether, 155
 Anæstheticus, 155
 Purificatus, 155
 Soap, 657
 Sulphuric, 155
 Ethylene, 166

- Æthylis Chaulmoogras, 575
 Chloridum, 169
 Affusion, cold, 36
Afin, 172
 Agar, 348
 Aglucone, 5, 266
 Agotan, 602
 Agropyrum, 709
 Agurin, 391
 Air Bath, 39
 Airol, 481
Ajowan ke tel, 706
 Ajowan oil, 706
 Albargin, 123
 Albumini Tannas, 367
 Albutannin, 367
 Alcohol, 141
 Dehydratum, 141
 Diluted, 141
 Alcoholism, 148
 Alepol, 575
 Alexandrian Senna, 355
 Alkalies, the, 66
 Alkaline bath, 38
 Alkaloids, 3
 Vegetable, 4
 Alkalosis, 626
Alkatra, 564
 Allergy, 50, 683
 Allobarbitone, 202
 Allonal, 205
 Allyl-thio-urea, 530
 Almond Oil, 650
 Alocol, 130
 Aloes, 351
 Aloin, 352
 Alsol, 130
 Alstonia, 705
 Alum, 130
 gargle, 130
 Alumini Aceto-tartras, 130
 hydroxidum, 130
 Alypin, 253
Amallus, 348
 Ambrine, 659
 American Wormseed Oil, 378
 Amidopyrine, 426
 Amines, 4
 Aminophylline, 391
 Aminoform, 396
 Ammoniated Mercury, 467
 Ammonii Bicarb., 90
 Bromidum, 209
 Carbonas, 90
 Chloridum, 91
 Iodidum, 501
 Mandelas, 399
 Picras, 563
 Salicylas, 431
 Ammonium, 87
 Ichthosulphonate, 582
 Sesquicarbonat, 90
 Amoebic infection, drugs used in, 512
 Ampoulæ, 36
 Amroids, 4
 Amydracaine hydrochlor., 253
 Amyl Nitrite, 297
 Amylase, 335
 Amylene Chloral, 191
 Hydrate, 198
 Amylocaine Hydrochlor., 253, 261
 Amyloform, 571
 Amylum, 656
 Amytal, 202
 Sodium, 207
 Anabin, 707
 Anæsthesia, preliminary, 166
 Infiltration, 260
 Intraspinal, 255, 258
 Regional, 255, 260
 Anæsthesine, 253
 Anæsthetics, general, 151
 local, 251
 Analgesic Balsam, 437
 Analgesics, 425
 Anaphrodisiacs, 406
 Anaphylaxis, 682
 Anarcotine, 174
 Andeer's Lotion, 563
 Anethum, 536
 Aneurin, 584
 Anhydrotics, 644
 Anhydrous Lanolin, 660
 Anodyne, Hoffman's, 155
 Local, 252
 Tincture, 174
 Antagonism, 51
 Anterior Pituitary, 420
 Anthelmintics, 372
 Anthracene Purgatives, 350
 Anthrax, Serum for, 681
 Antibacterial Sera, 679
 Anticatarrhal Salis, 527
 Anticholera Vaccine, 688
 Antidysentery Serum, 677
 assay of, 13
 Antiemetics, 336
 Antifebrin, 427
 Antigalactagogue, 406
 Antigen, 666
 Antilytic Serum, 682
 Antimalarial remedies, 442
 Antimenihgococcus Serum, 678
 Antimonii et Potassii Tartras, 505
 et Sodii Tartras, 505
 Antimonium Tartaratum, 505
 Antiparasitics, 546
 Antiplague Vaccine, 688
 Antipneumococcic Serum, 680
 Assay of, 13
 Antipyretics, 425
 Antipyrin, 426
 Acetyl-salicylas, 427
 Caffeine-citricum, 385

- Antipyrin Salicylate, 427
 Antirabic Vaccine, 689
 Antirachitic Vitamin D, 588
 Assay of, 13
 Antirheumatic, 431
 Antiseptic Cotton, 41
 Gargle, 41
 Gauze, 39
 Antiseptics, 546
 general, 547
 intestinal, 341
 pulmonary, 321
 urinary, 396
 Antisialogogues, 325
 Antispasmodics - bronchial, 318
 Antistaphylococcal Serum, 682
 Antithyroidin, 620
 Antitoxin Sera, 671
 Antitoxinum Diphthericum, 672
 Edematous, 676
 Staphylococcum, 677
 Tetanicum, 675
 Vibriosepticum, 676
 Webbmann, 676
 Antityphoid Vaccine, 688
 Antityphoid paratyphoid Vaccine, 688
 Anti-venom Serum, 678
 Antiviral, 666, 687
 Antrophores, 39
 Antutrin, 431
 Aolan, 695
 Aperients, 341
 Aphrodisiac, 406
 Apocodine Hydrochlor., 188
 Apocynum, 281
 Apomorphine Hydrochlor., 314
 Apple, Bitter, 360
 Aqua, 15
 Aromaticus, 16
 Destillata, 382
 Sterilisata, 16, 383
 Arabum, 7
 Arachis Oil, 652
 Argenti Nitras, 122
 Induratus, 122
 Argento proteinum Fotte, 122
 Mile, 122
 Argentum Colloidale, 122
 Argyria, 123
 Argyrol, 122
 Aristochin, 445
 Aristol, 557
 Aristosquimic, 445
 Arjuna, 709
 Aromatic Bitters, 328
 Sugars, 40
 Waters, 16
 Arrhenal, 494
 Arsacetin, 495
 Arsamum, 494
 Arsenic, 486
 Antidote, 632
 Arsenic Preparations of, 486, 492-494
 White, 486
 Arseno-benzol, 493
 Arspenamina, 493
 Argentica, 493
 Encephalitis, 497
 Artificial Cautsbad Salt, 344
 immunity, 665
 Asaletida, 531
 Aschheim-Zondek test, 421
 Ascorbic acid, 587
 Aspidium, 374
 Aspin, 431
 Aspirodine, 432
 Assay, biological, 11
 Asthma Powder, 80
 Astringent gargle, 41
 Local, 286
 Metals, 118
 Vegetable, 367
 Atelbrin, 462
 Musonate, 463
 Atophan, 602
 Atoxyl, 494, 511
 Atropina, 235
 Aurantii Cortex Recens, 330
 Siccatus, 330
 Auri et Sodii Chlor., 133
 Sodii thiosulphas, 133
 Avertin, 197
 Azadirachta Indica, 710

B

- Bablu, 706
 Bacteriophage, 670
 Bakas, 701
 Balnea, 36
 Balsams, 7
 Balsam, Analgesic, 437
 Friar's, 438
 of Copaiba, 400
 of Peru, 525
 of Tolu, 526
 Banisterine, 248
 Barbitol, 200
 Barbitalum Solubile, 201
 Barbitonum, 200
 Barii Chloridum, 107
 Sulphas, 107
 Bari Sanf, 537
 Barium meal, 107
 Sulphate, 107
 Sulphide, 108
 Baryta Sulphurata, 108
 Basal narcosis, 152, 166
 Bases, 4
 Basham's Mixture, 632
 Basilicon Ointment, 524
 Bassorin, 7
 Paste, 656
 Bath, 36

- Bath, Air, 39
 Cold, 36
 Hot, 37
 Medicated, 38
 Mineral water, 38
 Nauheim, 38, 305
 Neem, 38
 Russian, 39
 Temperature of, 39
 Turkish, 39
 Vapour, 39
 Bayer 205, 512
 B C. G. Vaccine, 693
 Beer, 142
 Yeast, 586
 Beeswax, white, 661
 yellow, 661
 Belæ Fructus, 701
Belati Kumrar bij, 708
 Belladonnæ Folia, 234
 Radix, 234
 Benzacoinine, 283
 Benzaldehyde Green, 570
 Benzamine Lactate, 254
 Benzedrine, 296
 Benzocaine, 253, 261
 Benzoinum, 437
 Benzonaphthol, 566
 Benzosol, 322
 Benzyl Benzoas, 438
 Berberis, 704
 Berberine Salts, 704
 Betaeucaine Hydrochlor, 253
 Beta-naphthol, 566
 Benzoate, 566
 Salicylate, 566
 Betel, 705
 Betol, 566
Bheranda tel, 349
Bhang, 190
 Biborate of Sodium, 572
 Bile, secretion of, 364
 Binodide of Mercury, 465
 Biological assay, 11
 B I P P, 481
Biranga, 708
 Bismarsen, 481
 Bismogenol, 481
 Bismuth, Preparations of, 479-481
 Bitters, Vegetable, 328
 Bitter Apple, 360
 Orange Peel, 330
 Black Draught, 355
 Haw, 424
 Wash, 467
 Bland's Pill, 632
 Bleaching Powder, 551
 Bliss's Cure, 80
 Blistering Liquid, 647
 Plaster, 647
 Blisters, 727
 spreading of, 727
 Blood, drugs acting on, 621
 Coagulation of, 624
 injection of, 624
 Reaction of, 625
 Toxicology of, 627
 Blood-pressure, Drugs raising, 285, 287
 lowering, 286, 297
 Blood-vessels, action on, 284
 Blue Mass, 465
 Ointment, 465
 Pill, 465
 Stone and Vitrol, 128
Boerhaavia diffusa, 703
Bol, *Bola*, 524
 Bolus, 39
 Bone-marrow, 621
 Borax, 572
 honey, 573
 Boric Acid, 572
 Borocaine, 254
 Bottles, dispensing, 712
 graduations of, 712
 label on, 711
 Bougies, 729
 Preparation of, 729
 of special drugs, 729
 Brain, drugs acting on, 140
 Bran Bath, 38
 Brandy, 142
 Brass Founder's Ague, 128
 Brilliant Green, 570
 Brodie's Gout Pill, 465
 Brometone, 209
 Bromides, 208
 Bromidia, 209
 Bromoformum, 209
 Bromol, 559
 Bromo Ray, 358
 Bromural, 201
 Bronchial antispasmodics, 318
 Secretion, action on, 308
 Sedatives, 320
 Broom tops, 395
 Brown Mixture, 655
 Bruising, 8
 Bucco, 402
 Buchu, 402
 Buginaria, 39
 Bulbocapnine, 247
 Burgundy, 142
 Burnett's Fluid, 126
 Butææ Semina, 708
 Butobarbital, 202
 Butyl-Chloral Hydras, 191
 Butyn, 254

C

Cacao Butter, 662
 Cachets, 39, 726
 Cacodylates, 494
 Cacodyliacoi, 494

- Caffeina, 385
 - Citras, 385
 - et Sodii benzoas, 385
 - et Sodii salicylas, 385
- Calamina, 127
- Calceterol, 588
- Calcii Acetyl salicylas, 431
 - Carbonas, 94
 - Chloridum, 95
 - Hydratum, 96
 - et sodii lactas, 97
 - Glycerophosphat, 136
 - Gluconas, 96
 - Hydroxidum, 102
 - Hypophosphis, 136
 - Iodobehenas, 557
 - Lactas, 96
 - Levyulinate, 96
 - Phosphas, 96
- Calcination, 8
- Calcinol, 234
- Calcium, 94
 - Duretin, 391
 - Permanganate, 549
- Calomel, 467
 - Cream, 467
 - Injection, 467
 - Ointment, 467
 - Vegetable, 362
- Calore rescents, 425
- Calumba, 328
- Calx Chlorinata, 551
 - Sulphurata, 581
- Camphor, 540
 - Monobromata, 541
- Camphorated Oil, 541
- Camphor, 630
- Canadian Hemp, 281
- Cane Sugar, 594
- Cannabine Tannas, 190
- Cannabis Indica, 189
- Cantharidin, 647
- Capillaries, action on, 285
- Caprokol, 399
- Capsici Fructus, 530
- Capsules, 39, 736
- Caraway Fruit, 535
- Carbamide, 393
- Carbarsone, 513
- Carbasa Antiseptica, 39
- Carbo Ligni, 339
- Carbolic Acid, 558
- Carbon Dioxide, 304
 - Bath, 305
 - Snow, 304
- Tetrachloride, 376
- Carbonic acid bath, 38, 305
 - gas, 164
- Cu bromatum, 201
- Cardamomum, 534
- Cardiac depressants, 281
 - tonics, 266
- Cardiazol, 164, 541
- Cardio-vascular system, action on, 263
- Cardhone, 541
- Carlsbad Salt, Artificial, 344
 - Water, 344
- Carminatives, 328, 533
- Carmine, 663
- Carotene, 583
- Carotid Sinus, 159, 285 *
- Caron Oil, 103
- Carum, 535
- Caryophyllum, 533
- Cascara Sagrada, 356
- Cassia, 348
- Castile Soap, 657
- Castor Oil, 349
- Cataphoresis, 45
- Cataplasmata, 16
- Catechu, 370
- Cathartics, See Purgatives, 341
- Caustics, 645
- Caustic, Lunar, 132
 - Potash, 68
 - Soda, 69
 - Toughened, 122
- Cephaline, 624
- Cera Alba, 661
 - Flava, 661
- Cerasin, 7
- Cerebral Depressants, 140
 - Stimulants, 140
- Cerebrum, action on, 140
- Cerevisie Fermentum, 586
- Chalk, 94
 - Mixture, 94
- Champagne, 142
- Chandani tel, 401
- Channels for administration, 43
- Chartas, 190
- Charcoal, 339
- Charta Nitrata, 80
- Chatham, 705
- Chaulmoogra Oil, 575
- Chebulic Myrobalsam, 707
- Chelsea Pensioner, 578, 600
- Chemical Food, 630
- Chemo-therapeutic agents, 440
- Chemotherapy, 2
- Chenopodium oil, 378
- Children, Prescription for, 60
- Chillie Paste, 531
- China badamer tel, 652
- Chinese White, 127
- Chinosol, 513
- Chinosol, 565
- Chiretta, 329 **किरिटा प. ४३**
- Chloral Camphoratum, 191
 - Formamide, 195
- Chloralamide, 195
- Chloralis Hydras, 191
- Chloralose, 191
- Chloramine, 551

- Chlorbutol, 195
 Chloretone, 195
 Chloric Ether, 153
 Chloride of Lime, 551
 Chlorinated Lime, 551
 Chlorine gargle, 78
 Chlorodyne, 153
 Chloroformum, 152
 Aconiti, 282
 Camphoratum, 153
 Cholagogues, 364, 365
 Purgatives, 361
 Cholera Vaccine, 688
 Choleretics, 364
 Choline, 233
 hydrochloride, 233
 Cholinergic, 222
 Chrismaline, 658
 Chromium Trioxide, 136
 Chrysarobin, 577
Chun, 102
 Ciliary muscle, action on, 224
 Cinchona, 442
 Febrifuge, 442
 Cinchonidinæ Sulphas, 442
 Cinchoninæ Sulphas, 443
 Cinchophenum, 602
 Cineole, 537
 Cinnamomum, 537
 Citric Acid, 109
 Citrine Ointment, 465
 Clove, 533
 Clysters, 40
 Coagulation of Blood, 624
 Coagulen, 624
 Cobra Venom, 679
 Cocaine, 252
 Hydrochlor., 252
 Coccus, 663
 Cochineal, 663
 Cocoa Butter, 662
 Cod-liver Oil, 590
 Codeina, 187
 Codeinæ Phosphas, 187
 Sulphas, 188
 Colchici Cormus, 600
 Semen, 600
 Colchicina, 600
 Colchicine Salicylate, 600
 Cold affusion, 36
 Bath, 36
 Compress, 39
 Douché, 37
 Sponging, 37
 Coli Vaccine, 690
 Collargolum, 122
 Collodion, 16, 661
 Flexile, 661
 Ichthammol, 582
 Collodium Belladonnæ, 234
 c Iodoformo, 556
 Salicylicum Co., 432
 Colloid metals, 117
 Collunaria, 39
 Collutories, 39
 Collyria, 39
 Collyrium aluminis, 130
 Colocynthis Pulpa, 360
 Colophony, 523
 Colsulanyde, 514
 Combination of Drugs, 55
 Explosive, 54
 Poisonous, 55
 Common Salt, 81
 Compound alkaline spray, 573
 Compress, cold, 37
 Condv's Fluid, 549
 Conessi Bark, 707
 Confections, 16
 Confectio Guaiaci Co., 578, 600
 Congo red, 624
 Conium, 250
 Conserves, 16
 Contraction of words, 738
 of phrases, 738
 Contramine, 579
 Contusion, 8
 Convalescent Sera, 666
 Convulsants, 214
 Copaiba, 400
 Oil, 400
 Resin, 400
 Coramine, 164, 541
 Cord, drugs acting on, 213
 Coriander Fruit, 535
 Corn Paint, 432
 Syrup, 595
 Corpus Luteum, 423
 Corrosive Sublimate, 466
 Cortin, 618
 Costus, the, 701
 Cotarnine Chloride, 174
 Cottonseed Oil, 650
 Couch Grass, 709
 Counter-irritants, 644
 Cowling's Rule, 48
 Cream, Calomel, 467
 Mercurial, 465
 of magnesia, 103
 of Tartar, 343
 Creams, Creamora, 39
 Creosotal, 321
 Creosote, 321
 Carbonas, 321
 Cresol, 562
 Cresyl Hydrate, 562
 Creta, 94
Crimidana, Cringdana, 663
 Crisalbina, 133
 Croton oil, 360
 Crude drugs, 3
 Crushed Linseed, 651
 Cryogenine, 438
 Crystallisation, 8

Cubebæ, 703
 Cucurbitæ Semina Preparata, 708
 Cumulative action, 51
 Cupri Sulphas, 128
 Cuprum Aluminatum, 128
 Curara, 249
 Curd Soap, 657
 Curschmann's Solution, 155
 Cure, Hinrod's, 80
 Cycloplegia, 224
 Cyclopropane, 167

D

Dakin's Solution, 551
Dalchini, 537
Dalchini, 704
 Deadly Nightshade leaves, 234
 Decoction, 713
 Decoction Belæ, 702
 Agropyri, 709
 Decoloration, 8
 Dehydrated Ethanol, 141
 Delirants, 141
 Demulcents, 649
 Demulcent gargle, 41
 Dentifrices, 324
 Deodorants, 546
 Depilatories, 644
 Derivatives, 647
 Dermatol, 481
 Desiccated Parathyroid Gland, 610
 Stomach, 630
 Thyroid, 606
 Desensitisation, 694
 Despumation, 8
 Detoxicated Vaccine, 665, 686
 Dextrose, 595
Dhania, 535
Dham lanka, 530
 Di-acetyl morphine Hydroch., 189
 Tannin, 387
 Diachylon Ointment, 119
 Plaster, 119
 Dial, 202
 Dialysis, 8
 Diamorphine Hydrochlor., 189
 Diaphoretics, 643
 Diaplyte Vaccine, 686
 Diastase, 335
 Dichloramina, 552
 Dicodid, 188
 Diethyl Malonyl-urea, 200
 Digalen, 267
 Digallic Acid, 367
 Digestion, 8
 Digestive Ferments, 331
 Digipuratum, 267
 Digitalin, 267
 Digitalis, assay of, 12
 Folium, 266
 Pulverata, 267
 Digitonin, 267

Digitoxin, 266
 Digoxin, 267
 Dilaudid, 175
 Dill, 536
 Dilling's Formula, 48
 Diluted Hydrogen Cyanide, 336
 Dimethyl ketone, 572
 Xanthine, 391
 Dimol, 565
 Dionin, 175
 Diosma, 402
 Diphtheria Antitoxin, 672
 Assay of, 13
 Prophylactic, 673
 Dipropyl Barbituric Acid, 201
 Direct action, 61
 Directions to patient, 59
 Disinfectants, 546
 Di-sodium Hydrogen Phosphate, 344
 methylarsonate, 494
 Dispensing, general directions for, 711
 Dissolution, law of, 140
 Distilled Water, 382
 Dita Bark, 705
 Diuretics, 381, 382
 classification of, 381
 saline, 395
 vegetable, 395
 Diuretin, 390
 Donovan's Solution, 465, 486
 Dornigene, 201
 Dormiol, 191
 Dose, adult, 47
 calculation of, 48
 factors modifying, 48
 maximum, 47
 minimum, 47
 Dover's Powder, 173, 309
 Drastic Purgatives, 358
 Draught, 41
 Dried milk, 595
 Drops, 41
 Drugs, acting on Blood, 621
 administration of, 43
 collection of, 3
 combination of, 55
 composition of, 3
 crude, 3
 habitat, 3
 how act, 61
 impurities of, 7
 sources of, 3
 standardisation, of, 11
 Dry Extract of Liver, 627
Dudhiabish, 281
 Duotal, 322
 Dupuytren's Pills, 477
 Dysentery Vaccine, 690

E

Easton's Syrup, 215, 444, 630

- Ecboics, 405
 Effervescent, Granular, 17
Elachi, 534
 Elæosacchara, 40
 Electuaries, 16
 Elegant prescription, 59
 Eleoptene, 6
 Elixiria, 17
 Elixir Diamorphinæ et
 Pini Co., 189
 Terpini c. Apomor-
 phina, 189
 Ephedrinæ Hydrochlor, 293
 of Vitrol, 113
 Ovo Lecithini, 599
 Papaini, 334
 Paregoric, 173
 Viburni et Hydrastis, 424
 Elutriation, 8
 Embelia, 708
 Embrocations, 23
 Emetics, 335
 Emetine Hydrochlor, 310
 Bismuth-iodide, 310
 Periodide, 310
 Emmenagogues, 405
 Emollients, 649
 Emplastra, 17
 Emplastrum Bellad. Fluidum, 234
 Plumbi Oleatis, 119
 Empyreumatic oils, 6
 Emulgents, 714
 Emulsifying agents, 714
 Emulsio Iodoformi, 556
 Olei Morrhuæ, 590
 c. Hypophosph., 590
 Paraffini et Kaolini, 132
 Emulsions, 714
 of special drugs, 716
 Enema opii, 184
 Enemata, enemas, 40
 Enepidermic, 44
 Enteric-coating, 725
 Enteroclysis, 40
 Entero-vioform, 513
 Entodon, 554
 Enzymes, 5
 Ephedrine Hydrochloride, 292
 Ephetonin, 296
 Epidermic medication, 44
 Epinephrine, 287
 Epsom Salts, 104, 345
 Ergamine, 406
 Ergometrine, 407
 Ergota, 406
 Præparata, 407
 Ergotamine, 407
 tartrate, 407, 412
 Ergotism, 411
 Ergotoxine, 406, 408
 Ethanesulphonate, 407
 Erythroxylis Tetranutras Dil., 301
 Escharotics, 645
 Eserine Salicylas, 229
 Essence of Ginger, 540
 Essential oils, 6, 26
 Ether, 155
 Chloric, 153
 Ethylic, 155
 Nitrous, spirit of, 394
 Soap, 657
 Sulphuric, 155
 Ethocaine Borate, 254
 Hydrochlor, 253
 Ethyl Aminobenzoate, 253
 Carbamate, 208
 Chaulmoograte, 575
 Chloride, 169
 Esters of hydnocarpus oil, 575
 Hydrocupreine hydrochlor, 460
 Morphine hydrochlor, 175
 Oxide, 155
 Ethylene, 166
 Ethylic Ether, 155
 Ethylsulphonal, 199
 Eucaine, 253
 Hydrochloride, 253
 Lactate, 254
 Eucalyptol, 527
 Eucalyptus Oil, 527
 Eukodal, 175
 Euonymus, 363
 Euonymin, 363
 Eupad, 552
 Euphthalmi, 235
 Euphylline, 391
 Euquinine, 445
 Euresol, 562
 Eusol, 551
 Evacuants, see Purgatives, 341
 Evipan, 202
 Sodium 202, 207
 Evalgin, 427
 Excipient for pills, 720
 Exhilarants, 141
 Expectorants, 308
 Explosive combinations, 54
 Expressed oils, 26
 Expression, 8
 Exsiccated Sod Carb., 70
 Extemporaneous Pharmacy, 1
 Extracts, 17
 Dry, 20
 Ethereal, 19
 Goulard, 118
 Liquid, 18
 of Liver, 627
 of ox-bile, 365
 Pituitary, 415
 Soft, 18
 Extractum Agropyri Liq., 709
 Beke Liq., 702
 Belladonnæ viride, 235
 Berberis, 704

Extractum Cannabæ, 189

Enonym, 363

Fellis Bovini, 365

Gründelia liq., 320

Hepatis Liq., 628

See, 627

Hydrastis Liq., 415

Indis, 363

Kirchi Liq., 707

Malti, 334

Peptonizæ Liq., 705

Pilularum Liq., 415

Pimaricæ Liq., 703

Suprarenali Cortex, 618

Viburni Liq., 424

Eye-action on, 223

ointments, 26

Eye-discs, 22

F

Ex Medicinis, 586

Fakir, 130

Fats, 5

Febrifuges, 425

Felamm, 397

Fel Bovinum Purificatum, 365

Fennel, 537

Ferments, 5

Ferr. Arsenas, 486

Cocculas, 494

et potassium, 633

Glycerophosph., 137

Hydroxide Magnesia

Oxide, 632

Iodidum, 633

Lactas, 633

Quinine et Strychnine Citras, 633

Sabicas, 432

Ferric's Salt, 481

Ferro-Somatose, 595

Ferrum, 630

Preparations of, 630-633

Ferry's Antitoxic Serum, 678

Felix-Mas, 374

Filtration, 733

Fixed oils, 5, 26

Flavouring agents, 533

Flax Seeds, 651

Flexible Collodion, 661

Flowers of Sulphur, 578

Fluid Magnesia, 104

Fluorescimum Soluble, 568

Fornicium, 537

Fomenta, 40

Foot Bath, hot, 38

Formaldehyde, 571

Formanol, 397

Formin, 396

Formol, 571

Formolised Vaccine, 686

Fournier, 309, 512

Fowler's Solution, 486

Freezing Mixture, 37

Friar's Balsam, 438

Fructose, 597

Fuadm, 510

Fumigation, 41

Fusion, 8

G

Gach march, 530

Galactogogues, 405

Gambir, 370

Gand, 655

Gandhabol, Gandharasha, 524

Gauja, 189

Gardenal, 201

Gargarisma aluminis, 130

Chlori, 78

Gargarismata, 41

Garrick's Lozenges, 579

Gas-gangrene Antitoxin, 676

assay, of 13

Gas, Carbon Dioxide, 304

Laughing, 168

Nitrous Oxide, 168

Oleant, 166

Oxygen, 306

Gaster Sicca, 630

Gastric juice, action on, 327

functions of, 326

movement, action on, 328

sedatives, 328

Gavano, 310

Gelanthum, 656

Gelatin, 598

coating, 724

paste, 20

Gelatinum, 20, 598

Zinci, 20, 127, 598

Gelsemium, 251

General anesthetics, 151

Genital organs, drugs acting on, 404

Gentian, 329

Violet, 570

Germann, 512

Gestone, 423

Gin, 142

Gingell Oil, 650

Ginger, 540

Glacial acetic acid, 108

Glauber's Salt, 344

Glucanth, 721

Glucocloral, 191

Glucose, 595

Saline Solution, 81

Glucosides, 5

Glusidum soluble, 663

Glutoid coating, 725

Glycerins, 20, 652

Glycerinum, 652

Glycerinum Aluminis, 130
 c. aqua rosæ, 653
 Papaini, 334
 Pepsini, 333
 Plumbi Subacetatis, 121
 Glycerophosphates, 136
 Glycine, 232
 Glucosides, 5
 Glycyrrhizæ Radix, 654
 Glymol, 658
 Gold, 133
 Golden Seal, 414
 Gonococcus Vaccine, 690
 Goodeve's Mixture, 104
 Gossypia Antiseptica, 41
 Goulard's Extract, 118
 Lotion, Water, 118
 Grain, division of, 713
 Granulation, 8
 Grape Sugar, 595
 Green Iodide of Mercury, 466
 Mountain Cure, 80
 Soap, 657
 Gregory's Powder, 354
 Grey Oil, 465
 Powder, 465
 Griffith's Mixture, 632
 Grindelia, 320
 Ground Nut Oil, 652
 Guaiacamphol, 322
 Guaiaci Resina, 599
 Guaiacol, 321
 Benzoas, 322
 Cacodylas, 494
 Camphorate, 322
 Carbonas, 322
 Cinnamate, 322
 Guanidine, 617
 Guaranine, 385
 Guinea Pepper, 530
 Gums, 7
 Gum Acacia, 655
 Benjamin, 437
 resins, 7
 Guttæ, 41
 Pilocarpinæ, 225
 Guy's Pill, 267, 281, 465
 Gynocardia Oil, 575

H

Habit, 49
 Hæmatics, 632
 Hæmostatics, 286
 Hair, action on, 644
 Halibut-liver oil, 593
 Hamamelis, 371
 Hard Paraffin, 658
 Soap, 657
Haritaki, 707
 Harmine, 248

Hashish, 190
 Haustus, 41
 Heart, drugs acting on, 263
 Heart-rate, drugs altering, 265
 Heavy Magnesia, 103
 Magnesium Carb., 104
 Metals, 116
 Hebra's Ointment, 119
 Helmitol, 397
 Hemlock Leaves, 250
 Hemp, Canadian, 281
 Indian, 189
 Henbane Leaves, 245
 Heparin, 625
 Hepatex-T, 630
 Heroin Hydrochlor., 189
 Herxheimer reaction, 497
 Hesperidin, 594
 Hexamethylenetetramine, 396
 Hexamine, 396
 Glycocholate, 397
 Hexyl-Resorcinol, 379, 399
 Humrod's Cure, 80
Hing, 531
 Hippo, 309
Hirakas, 632
 Hirudin, 625
 Histamine, 406
 Acid Phosphate, 327, 413
 Histidine hydrochlor., 414
 Hoffmann's Anodyne, 155
 Homatropinæ Hydro-
 bromidum, 235, 245
 Honey, Purified, 654
 Hormonal, 621
 Hormones, 5
 Horse Serum, Normal, 682
 Hot Bath, 37
 Compress, 41
 Douche, 39
 Sponging, 39
 Human milk, artificial, 595
 Hutchinson's pill, 174, 465
 Hydnocarpus Oil, 574
 Hydrargyri chloridum mitis, 467
 Hydrargyrum, 465
 Preparations of, 466-468
 Hydrastina, 415
 Hydrastinæ Hydrochlor., 415
 Hydrastis, 414
 Hydrobromic Acid, 209
 Hydrochloric Acid, 110
 Hydrogen-ion concentration, 65
 Hydrogen Oleate, 660
 Peroxide Solution, 548
 Hydrophobia, treatment of,
 See Antirabic Vaccine, 689
 Hyoscinæ Hydrobrom., 246
 Hyoscyamus, 245
 Hypertonic Saline Solution, 85
 Hypnotics, 169
 Hypodermoclysis, 45

I

Iatroleptic medication, 44
 Ichthallum, 582
 Ichthammol, 582
 Colloidon, 582
 Suppositories, 582
 Ichthyol, 582
 Idiosyncrasy, 49
 Immunity, Acquired, 664
 Active, 665
 Artificial, 665
 Local, 666
 Natural, 664
 Passive, 665
 Immunogens, 686
 Imperial Drink, 343
 Ince's precaution, 721
 Incompatibility, 52
 Chemical, 52
 Physical, 52
 Physiological, 54
 Indian Hemp, 189
 Podophyllum, 361
 Indicarminum, Indigo-carmin, 403
 Indirect action, 61
Indiaturum, 360
 Inhalation anaesthesia, 260
 Infusion, 21, 713
 Concentrated, 21
 Fresh, 21
 Infusum Alstoniae, 705
 Azadirachtæ, 710
 Chirate, 330
 Kurchi, 707
 Scoparii Rec., 395
 Inhalatio Iodi Co., 323
 Injections, 33
 Intracardiac, 47, 391
 Intradermal, 45
 Intramuscular, 45
 Intraspinal, 47
 Intravenous, 46
 Intraventricular, 47
 Rectal, 40, 44
 Subcutaneous, 45
 table of, 22
 Injectio Camphoræ, 541
 Æthereæ, 155
 Ferri et arseni, 633
 Hydrarg. Fort., 465
 Mersalvii, 391, 468
 Novocainæ et Adrenalinæ, 253
 Sodii Chloridi et Acaciæ, 81, 655
 Salicylatis, 432
 Thiosinamæ et Sod. Salicyl., 530
 Inoculation, 45
 Insufflatio Bismuthi et Morphina, 481
 Menthol et Cocainæ, 544
 Insufflations, 41
 Insulin, 612
 assay of, 12

Insulin Protamine-Zinc, 616
 retard, 616
 Intestinal Antiseptics, 341
 Intestines, action on, 339
 Intracardiac injection, 47, 291
 Intracutaneous injection, 45
 Intradermal administration, 45
 Intramuscular injection, 45
 Intra-ocular tension, action on, 225
 Intraspinal anaesthesia, 258
 injection, 47
 Intravenous injection, 46
 Intraventricular injection, 47
 Inunction, 44, 477
 Iodides, 501
 Iodine, 553
 Iodipin, 323
 Iodised, oil, 323
 Phenol, 555, 559
 Iodism, 502
 Iodo-caffeine, 385
 Iodo-Ray, 358, 366
 Iodotorm, 556
 Iodol, 557
 Iodophthaleinum, 366
 Iodo-theobromin, 391
 Ionic medication, 45
 Theory, 64
 Ipecacuanha, 309
 Ipomœa, 358
 Iridin, 363
 Iris, action on, 223
 Iron, 630
 and arsenic injection, 633
 Irritants, 644
 Ispaghula, 709

J

Jaiphal, 538
Jalap, 359
 Orizaba, 358
Jasthimadhu, 654
Jira, 535
Jovaner tel, 706
Jujubes, 41
Juniper Tar Oil, 526

K

Kabab chini, 703
Kaladana, 702
 Resin, 703
Kamala nembur khosa, 330
Kaolin, 132
 excipient, 721
 Mass, 132
 poultice, 16, 132
Karpur, 540
Kasauli Antivenene, 679
Katbisk, 281
Kathi, 370
Katki, 705
Kayaputi ke tel, 528

- Kephir, 595
 Keratin Coating, 724
 Kerocaine, 353
Khari, 94
Khayer, 370
 Kidneys, action on, 379
 Koumiss, 595
 Krameria, 371
Kuchila, 314
 Kurchi Cortex, 707
 Kurchibine, 707
 Kurchi Bismuth Iodide, 707
 Kut, 701
- L
- Lacarnol, 620
 Lactic acid, 115
 Lactolan, 695
 Lactose, 594
 Lævulose, 597
 Lamellæ, 22
 Lanolin, 660
 Lapis Divinus, 138
 Lard, 660
 Lassar's Paste, 127
 Laudanum, 173
 Laughing gas, 168
 Lavandulæ Oleum, 539
 Lavements, 40
 Law of Dissolution, 140
 Laxatives, 348
 Lead Acetate, 118
 amblyopia, 120
 encephalopathy, 120
 Sugar of, 118
 Tetra-ethyl, 121
 Lecithin, 599
 Leeches, 286
 Leishmaniasis, drugs used in, 505
 Leiter's Coil, 37
 Lemon Peel, 536
 Levigation, 8
 Light Magnesia, 103
 Mag Carb, 103
 Lime, Slaked, 102
 Water, 102
 Limonade Purgative, 104
 Limonis Cortex, 536
 Linctus, Lincture, 41
 Codeinæ, 188
 Diamorphinæ c. Ipecac., 189
 Morphine, 174
 Pini, Terpin et Heroin, 523
 Linimenta, Liniments, 23
 table of, 23
 Linimentum Aconiti Oleosum, 282
 Calci, 649
 Camphoræ Co., 541
 Chloroformi, 541
 Exsiccans, 656
 Iodi, 554
 Methyl Salicylatis, 437
 Linimentum Sinapis, 529
 Linseed Meal, 651
 Oil, 651
 Tea, 652
 Linum, 651
 Contusum, 651
 Lipins, 6
 Lipodol, 323
 Lipoids, 6
 Lipo-Latin, 423
 Lipo Vaccine, 665
 Liquefaction, 8
 Liquid Glucose, 595
 Paraffin, 658
 Petrolatum, 658
 Liquores, liquors, 23
 table of, 23, 24
 Liquor Acidi Hypochlorosi Co., 551
 Ammonii Acetatis Dil., 93
 Fort., 93
 Citratis Dil., 93
 Ammonii Fort., 87
 Dil., 88
 Antisepticus, 324, 545
 Auri et Arsenii Brom., 133
 Bismuthi et ammonii citras, 481
 Bromidi Co., 209
 Calci Hydroxidi, 102
 Carbonis Detergens, 564
 Chlori, 552
 Dextrosi et Sod. Chloridi, 81
 Euonymi et Iridini, 363
 Ferri et Ammon. Acet., 632
 Hypophosph., 633
 Formaldehydi, 571
 Glycerolis Trinitratis, 300
 Hepatis Purificatus, 628
 Hydrogenii Peroxidi, 548
 Iodi Co., 554
 Decolor., 554
 Magnesii Bicarbonatis, 104
 Citratis, 104
 Opii Sedativus, 174
 Pancreatis, 333
 Pancreatini, 333
 Pepticus, 332
 Phosphori Co., 136
 Pituitarii, 415
 Plumbi Subacet., 118
 Potassii Hydroxidi, 68
 Permang., 549
 Ringer, 81
 Ringer-Locke, 81
 Santali Co., 402
 Saponis æthereus, 657
 Sodæ Chloridi Phvs., 81
 Chlorinate Chirurgicæ, 551
 Sodii Ethylatis, 87
 Thymolis Co., 545
 Liquorice, 654
 Listerine, 324, 545
 Litharge, 118

Litharge Plaster, 119
 Lithu carbonas, 93
 Citras, 93
 Lithontriptics, Biliary, 364
 Urinary, 382
 Liver, action on, 363
 Extract of, 627
 of Sulphur, 581
 Lixivation, 8
Loban, 437
Lobanga, 533
 Lobelia, 318
 Lobeline hydrochlor, 318
 Local action, 61
 anesthetics, 251
 anodynes, 252
 immunity, 666
 Loch, 41
Loha, 630
 Lotiones, lotions, 25
 Loto Ammoni Chloridi, 91
 Calamine, 127
 Calcis Sulphurati, 582
 Evaporans, 91
 Pisces Carb et Plumbi, 119
 Lozenges, 31, 730
 Lugol's Solution, 554
 Lummal, 201, 207
 Sodium, 201
 Lunar Caustic, 122
 Lysol, 562

M

M. and B. 125, 515
 M. and B. 693, 515, 518
 Maceration, 8, 730
Macher tel, 590
 Magma Ferri Hydroxidi, 632
 Magnesia, preparations of, 103-104
 Magnesi Perhydrol, 548
 Peroxidum, 548
 Sulphas, 104, 345
 Magnesium Sulphate Paste, 105
 Trisilicate, 104
 Magsoberent, 104
Makhal phal, 360
 Malachite Green, 570
 Male Fern, 374
 Malonurea, 200
 Malophen, 397
 Mammary glands, the, 423
 action on, 405
 Mandelic acid, 399
Mandl's Paint, 554
 Manganese Butyrate, 549
 Manna, 349
 Marc, 8
 Margosa Bark, 710
 Margosic Acid, 710
 Marinite, 586
 Marrubin, 621
Mashina, 651

Mass, Blue, 465
 Vallot's, 631
 Massa Ferri Carb, 631
 Hydragry, 465
 Massic Masses, 42
 Materia Medica Proper, 1
 Measures, 9
 in prescription, 55
 Medicated Baths, 38
 Mednal, 201
 Melon Pumpkin Seeds, 708
 Mel Depuratum, 654
 Mella, Mellita, 25
 Melting, 8
 Menthol, 544 *Mand*
 Mentholate, 544
 Menthyl Valenianate, 544
 Merbaphen, 468
 Mercurial Cream, 465
 erethismus, 473
 ointments, 36
 Mercurialised Serum, 478
 Mercuric chloride, 466
 iodide, 465
 oxycyanide, 467
 Mercuriochrome, 468
 Mercury, 465
 oleated, 466
 Mersalyl, 468
 Metabolism, action on, 604
 Metalloids, 136
 Metals, Collodial, 117
 Heavy, 116
 Metaphen, 468
 Methenamma, 396
 Methyl Acetanilide, 427
 Ditannin, 368
 Morphine, 187
 Salicylas, 437
 Sulphonat, 199
 Thionine Chloride, 569
 Methylated Spirit, 141
 Methylene Blue, 569
 Mexican Scammony, 358
 Migramme, 385
 Mild Protargin, 122
 Milk, action on, 405
 Artificial Human, 595
 Dried, 595
 of Sulphur, 579
 of Thyroidectomised goat, 620
 Peptonised, 333
 Sterile, injection of, 695
 Sugar, 594
 Minderer's Solution, 93
 Mineral oils, 6
 Minim, division of, 713
 Mistura Alba, 104
 Bismuthi Co. c Pepsino, 332
 et Morphina, 332
 Crete, 94
 Co., 94

Mistura Diuretica, 75
 Ferri Co., 632
 Guaiaci, 599
 Opii et Glycyrrhizæ Co., 655
Mitha kaduka bij, 708
 Mixed Vaccine, 665
 Mixtures, 25
 Mixture, Basham's, 633
 Brown, 655
 Chalk, 94
 compounding of, 714
 Griffith's, 632
 Potassi Acetatis Co., 75
 Red, 104
 Mocassin Venom, 625, 679
 Moebius's Serum, 620
 Mollinum, 42
 Mom, 661
 Monk's Hood, 281
 Moogrol, 575
 Moranyl, 512
 Morphine hydrochlor, 174
 preparations, 174
 Morrhue Oleum, 590
 Mouth, drugs acting on, 324
 Washes, 324
 Mucilages, Mucilages, 25
Mudra sung 118
 Muriatic Acid, 110
Musabar, 351
 Muscarine, 225
 Muscle extract, 620
 Mutton Suet, 660
 Mydriatics, 224
 Myocrisin, 133
 Myotics, 224
 Myristica, 538
 Myrobalanum, 707
 Myrrha, 524

N

Naphthalol, 566
 Naphthol, 566
 Narcotics, 151
 Narcotina, 174, 183
 Nauheim bath, 38, 305
 Nauseant expectorants, 309
 Nebulæ, 42
 Nebula Adrenalinæ Arom., 287
 et Cocaina, 287
 et Ephedrinæ, 293
 Alkalina Co., 573
 Cocainæ Co., 544
 Eucalyptols Co., 527
 Mentholis et Thymolis Co., 544
 Needle bath, 37
 Neem Bark, 710
 Bath, 38
 Nembutal, 202, 207
 Neocarsphenamina, 492
 assay of, 12

Neocinchophen, 602
 Neonol, 202
 Neosalvarsan, 492
 Neostibosan, 506
 Neotrepol, 481
 Nepenthe, 174
 Neptal, 468
 Nerve blocking, 255
 Nervous system, Drugs acting on, 139
 Neutral principles, 4
 New Cacodyle, 494
 Urotropine, 397
 Nicotine, 249
 Nicotinic Acid, 586
 Niemeyer's pill, 465
 Nirvanol, 201
Nishedal, 91
 Nitre, purified, 79
 Nitric Acid, 111
 Nitritoid reaction, 497
 Nitrogen Monoxidum, 168
 Nitroglycerin Tablets, 301
 Nitrous oxide, 168
 Normal Saline Solution, 81
 Serum, 682
 Novarsenobenzol, 492
 Novasurol, 468
 Novocaine, 253, 261
 Nuclein, 586
 Nucleol, 586
 Nupercaine, 261
 Nutmeg, 538
 Nut-oil, 652
 Nutrients, 583
 Nux Vomica, 214
 Pulverata, 215

O

Oculenta, 26
 Oculentum Atropinæ et cocainæ, 235
 Œstrin, 422
 Œstroform, 422
 Official Pharmacy, 1
 Preparations, 14
 Oil, American Wormseed, 378
 Camphorated, 541
 Castor, 349
 Codliver, 590
 Emyreumatic, 6
 Essential, 6, 26
 Fixed, 5, 26
 Grey, 465
 Gynocardia, 575
 Halibut-liver, 593
 Juniper tar, 526
 Mineral, 6
 of Cade, 526
 of Dill, 536
 of Eucalyptus, 527
 of Lavender, 539
 of Nutmeg, 538

- Oil of Peppermint, 539
 of Pine, 523
 of Sandal Wood, 401
 of Siberian Fir, 523
 of Theobroma, 662
 of Turpentine, 520
 of Wintergreen, 437
 Ptychotis, 706
 Volatile, 6, 26, 518
 Oil sugars, 40
 Ointment, Basilicon, 524
 Blue, 465
 Calomel, 467
 Citric, 465
 Compounding of, 731
 Diachylon, 119
 Hebra's, 119
 Prophylactic, 467
 Scott's, 465
 White Precipitate, 467
 Wilkinson's, 578
 Ointments, 35, 731
 Old Tuberculin, 691
 assay of, 13
 Olea, Oils, 5, 26
 Oleata, 26
 Oleatum Hydrargyrum, 466
 Olefant gas, 166
 Oleic-Acid, 660
 Oleo resins, 7
 Oleoresina Aspidii, 375
 Oleum Abietis, 523
 Ajowan, 706
 Amygdalic, 650
 Anethi, 536
 Anisi, 536
 Arachis, 652
 Cadinum, 526
 Cajuputi, 528
 Cari, 535
 Carvophylli, 533
 Cassia, 537
 Chaulmoogra, 575
 Chenopodii, 378
 Cinereum, 465
 Cinnamomi, 537
 Copaiba, 400
 Coriandri, 535
 Crotonis, 360
 Cubebæ, 703
 Decline, 658
 Eucalypti, 527
 Gossypii Sem., 650
 Hippoglossi, 593
 Hydnocurpi, 574
 Æthvlicum, 575
 Iodisatum, 27, 323
 Jecoris Aselli, 590
 Juniperi, 395
 Lavandulae, 539
 Limonis, 537
 Lini, 651
 Oleum Menthae Piperitæ, 539
 Morrhuae, 590
 Myristicae, 538
 Olivæ, 649
 Ricini, 349
 Rosmarini, 529
 Santal, 401
 Australiensis, 401
 Sesami, 650
 Sinapis Volatile, 529
 Terebinthinæ, 520
 Theobromatis, 662
 Tigli, 360
 Olive oil, 649
 Soap, 657
 Omnopon, 174
 Onum Water, 706
 Opacine, 366
 Opium, 172
 Preparations of, 173
 Pulveratum, 173
 Opodeldoc, 42, 657
 Optochin Hydrochloride, 460
 Orange Peel, 330
 Organic Arsenic Preparations, 491
 Orizaba Jalap-root, 358
 Orphol, 481
 Orthocaine, 253, 261
 Orthoform, 253
 Ostelin, 590
 Ourari, 249
 Ovary, the, 421
 Ovo-lecithin, 599
 Ox-bile, 365
 Oxidising agents, 548
 Oxygen, 306
 Oxymel, 108, 654
 Oxytocics, 405
 Oxytocin, 415
 Ozone paper, 80
- P
- Paints, 42
 Palash bij, 708
 Pale Catechu, 370
 Pan, 705
 Panama Bark, 317
 Pancreatin, 333
 Pantopon, 174
 Papaveratum, 174
 Papaverine, 183
 Sulphate, 175
 Papam, 334
 Papayar ata, 334
 Paraffinum Durum, 658
 Liquidum, 658
 Molle album, 659
 Flavum, 659
 Paraform, 572
 Paraformaldehydum, 571
 Paraldehyde, 196
 Parasitocides, 546, 577

- Parasympathetic system,
 action on, 220, 223
 Parathormone, 610
 Parathyroid, extract, 610
 Paregonic, 173, 541
 Elixir, 173
 Paroleine, 658
 Parrish's Syrup, 630
 Pasta, Pastes, 27
 Bismuthi et Iodoformi, 481
 Ichthammol, 582
 Potasæ et Calcis, 69
 Zinci Oxidi Co., 127
 Paste, Bassorin, 656
 Chillie, 531
 Lasar's, 127
 Unna's, 20, 127, 598
 Vienna, 69
 Zinc, 127
 Pastillus, Pastil, 42
 Patient, directions to, 59
 Pea-nut oil, 652
 Pearl coating, 724
 Pectin, 7
 Pediculi, action on, 577
 Pelletierinæ Tannas, 375
 Pencils, 42
 Pentamethylenetetrazol, 541
 Pentobarbital sodium, 202
 Pentothal sodium, 202
 Pepo, 708
 Pepper, Guinea, 530
 Pod, 530
 Pepsin, 331
 Peptone, 333, 694
 Peptonised Milk, 333
 Peptonising Powder, 333
 Per-Abrodil, 403
 Percaine, 261
 Perchloride of Mercury, 466
 Percolation, 9, 730
 Perles, 42
 Permanganate of Potassium, 549
 of Calcium, 549
 Pernocton, 207
 Pertussis Vaccine, 690
 Pessaries, Pessi, 42, 729
 Petroleum Jelly, 659
 Phanodorm, 202
 Pharbitis Seeds, 703
 Pharmaceutical processes, 8
 Pharmacy, 1
 Pharmacodynamics, 1
 Pharmacognosy, 1
 Pharmacology, 1
 Pharmacopœial preparations, 14-36
 Pharmacopœia, British, 7
 Phenacetinum, 426
 Phenazonum, 426
 Phenazoni Salicylas, 427
 Phenobarbital, 201
 Phenobarbitonum, 201
 Phenol, 558
 Camphor, 559
 Iodisatum, 559
 Iodised, 555, 559
 Red, 404
 Phenolphthalein, 357
 Phenolsulphonphthalein, 404
 Phenyl Acetamide, 427
 Alcohol, 558
 Ethyl Hydrantoin, 201
 Salicylate, 567
 Phosphoric Acid, 112
 Phosphorus, 136
 Physiological saline solution, 81
 Phylacogen, 665
 Physostigminæ Salicylas, 229
 Picric acid, 563
 Picrorhiza, 705
 Pigmenta, Pigments, 42
 Pigmentum Acidi Borici, 572
 Chrysarobini, 577
 Iodi Co., 554
 Iodoformi, 556
 Pill, Blaud's, 632
 Blue, 465
 Brodie's, 465
 coating, 724
 compounding of, 719
 Cutting, 721
 Dupuytlen's, 477
 Excipients, 720
 Guy's, 267, 465
 Hutchinson's 174, 465
 Niemeyer's, 465
 Plummer's, 467
 Rolling and rounding of, 721
 Silvering, 724
 Varnishing, 725
 Pilocarpinæ Nitræ, 225
 Pilocarpine Hair Lotion, 225
 Pilulæ, Pills, 27
 Pilula Colchici et Hydrarg. Co., 465
 Digitals Co., 267, 465
 Ferri, 632
 Hydrarg. c. Creta et Opii, 174, 465
 Subchloridi Co., 467
 Ovo-licithini, 599
 Phosphori, 136
 Plumbi c. Opii, 119, 173
 Pine, Oil of, 523
 Pine Tar, 564
 Pinol, 523
 Piperazin, 397
 Pitocin, 415
 Pitressin, 415
 Pituitary, anterior, 420
 Extract, 415
 assay of, 13
 Pix Carbonis Præparata, 564
 Liquida, 564
 Pini, 564
 Plasma, function of, 625

- Plac machine, 461
 Plasters, 17, 728
 Plumbi Acetas, 118
 Monoxidum, 118
 Plummer's Pill, 467
 Pneumococcus Vaccine, 690
 Podophyllum, 361
 Indicum, 361
 Resina, 362
 Podophyllum, 362
 Pod Pepper, 530
 Poison Nut, 214
 Poisonous combination, 55
 Poisons Act Indian, 734
 Polyvalent Vaccines, 665
 Potassa Caustica, 68
 Sulphurata, 581
 Potassa Acetas, 75
 Bicarbonas, 69
 Bromidum, 208
 Carbonas, 69
 Chloras, 77
 Citras, 75
 Guanicolsulphonas, 322
 Hydroxyquinolm sulphas, 565
 Hydroxidum, 68
 Iodidum, 501
 Nitras, 79
 Permanganas, 549
 Tartas Acidus, 343
 Potassium, 67
 antimonyl tartrate, 505
 bitartrate, 343
 Potentiation, 52
 Potus Imperialis, 343
 Poultices, 16
 Powders, 28, 725
 Precipitated Bismuth, 480
 Calcium Carbonate, 94
 Sulphur, 579
 Prepared Coal Tar, 564
 Prescribing, art of, 55
 Prescriptions, directions in, 711
 dispensing of, 712
 elegant, 59
 for children, 60
 position of, 712
 reading of, 711
 repetition of, 712
 weights and measures in, 55
 writing of, 57
 Primary action, 61
 Proctor's Paste, 721
 Procaine Hydrochlor., 253, 261
 Prolavine, 570
 Progesterone, 422
 Progonon, 423
 Prolin A & B, 421
 Proluton, 423
 Prontosil, 514
 Album, 514
 Rubrum, 514
 Prontosil Soluble, 514
 Prophylactic ointment, 467
 Propenal, 201
 Proseptasine, 515
 Prostates, The, 423
 Prosthigmine, 232
 Protamine Insulin, 616
 Zinc Insulin, 616
 Protargol, 122
 Protein Therapy, 694
 Protochloride of Mercury, 466
 Prun Virginianæ Cortex, 320
 Prunus Scrotina, 320
 Prussic Acid, dilute, 336
 Psoralea Corvillonia, 706
 Psychotic Oil, 706
 Pulmonary antiseptics, 321
 Pulping, 9
 Pulverata, Pulveres, 28
 Pulvis Acacia Co., 720
 Barii Sulphatis Co., 107
 Belladonnae, 234
 Butere Sem., 708
 Calcis Chlorinatae et
 Acidi Borici, 552
 Chiniosom, 513
 Effervescens Co., 344
 Ipecacuanhae, 309
 Co., 173, 309
 Jalape, 359
 Kaladana Co., 702
 Kino Co., 174
 Lobelia Co., 80
 Nucis Vomice, 215
 Opi, 173
 Pancreatini Co., 333
 Pectoralis, 655
 Pepsi Co., 332
 Soda Tartarate Effervescens, 344
 Soda Chloride Co., 573
 Vitamin B₁, 29, 584
 Pumiline, 523
 Punarnava, 703
 Pupil, action on, 223
 Purgatives, 341
 anthracene, 350
 cholagogue, 361
 classification of, 343
 drastic, 358
 hypodermic, 343
 saline, 343
 Purgen, 357
 Purified Borax, 572
 Honey, 654
 Nitre, 79
 Ox Bile, 365
 Pustulants, 645
 Pyramdon, 426
 Pyridium, 397
 Pyroxylinum, 661
 Pyocyaneus Vaccine, 690

Q

Quassia, 329
 Quicksilver, 465
 Quillaia, 317
 Quinby, 481
 Quinidinae Sulphas, 458
 Quinina, 445
 Preparations of, 444-445
 Quininae et Urea Hydrochloride, 393
 Bismuth Iodide, 481
 Bisulphas, 444
 Salacetas, 445
 Urethane, 445
 Quinophan, 602
 Quinoxyl, 513

R

Rabies, treatment of, 689
 Radium, 698
 Radon Seeds, 700
 Rasot, 704
 Rectified Spirit, 141
 Red Corpuscles, action on, 622
 Gourd Seeds, 708
 Mercuric Iodide, 465
 Mixture, 104
 Peruvian Bark, 442
 Reduced Iron, 631
 Refined Sugar, 594
 Reflex expectorants, 308
 Regional anæsthesia, 255, 260
 Remote action, 61
 Rennet, Rennin, 332
 Resin ointment, 721
 plaster, 524
 Resina, 523
 Guaiaci, 599
 Kaladanae, 703
 Podophylli, 362
 Scammonia, 358
 Resins, 7
 Resorcin Monacetate, 562
 Resorcinol, 562
 Respiratory System, action on, 302
 Reticulo-endothelial System, 440
 Revulsives, 647
 Rhamni Purshiani Cortex, 356
 Rhatany Root, 371
 Rhei Rhizoma, 353
 Rhodallin, 530
 Rhodan Calcium Diuretin, 391
 Rhubarb, 353
 Ringer's Solution, 81
 Ringer-Locke solution, 81
 Rivanol, 513
 River Bath, 37
 Rochelle Salt, 343
 Rubefacients, 645
 Rubrum Scarlatinum, 571

Russian Bath, 39

S

Saccharated Iron Carb., 631
 Saccharinum Soluble, 663
 Saccharomyces Cerevisiae, 586
 Saccharum Lactis, 594
 Purificatum, 594
 Sacred Bark, 356
 Sajodin, 557
 Sal Ammoniac, 91
 Volatile, Spirit of, 90
 Salacetol, 432
 Sal Carolinum Fact., 344
 Salicinum, 432
 Salicylic Acid, 431
 Saline Diuretics, 395
 Expectorants, 309
 Purgatives, 343
 Solution, Normal, 81
 Hypertonic, 85
 Salipyrin, 427
 Salivary Secretion, 335
 Salol, 567
 Varnishing, 725
 Salophen, 432
 Salt, Calsbad, 344
 Common, 81
 Epsom, 104, 345
 Glauber's, 344
 of Tartar, 69
 Rochelle, 343
 Seignette's, 343
 Saltpetre, 79
 Paper, 80
 Salts, 4
 Salvarsan, 493
 Salvarsanised Serum, 501
 Salve Mulls, 42
 Salyrgan, 468
 Sandal-wood Oil, 401
Sankha, Sanko, 486
 Sanocrysin, 133
 Santonin, 373
 Sapo Animalis, 657
 Durus, 657
 Mollis, 657
 Saponimenta, 42
 Saponins, 5, 316, 716
 Sapotoxins, 5, 317
Saptaparna, 705
 Sarcolan, 621
 Saussurea Lappa, 701
 Scaling, 9
 Scammonia Resina, 358
 Scarlet Red, 571
 Schick Control, 672
 Test Toxin, 672
 Scilla, 280
 Sclavo's Serum for Anthrax, 681
 Scoparium, 395

- Scopolamine Hydrobromide, 246
 Scott's Dressing and Ointment, 465
 Sea bath, 38
 Secale Cornutum, 406
 Secondary action, 61
 Sedasprin, 432
 Sedative, Bronchial, 320
 expectorants, 308
 gastric, 328
 uterine, 424
 Seidlitz Powder, 344
 Serignette's Salt, 343
 Senega, 316
 Sennae Folium, 355
 Fructus and Pods, 355
 Sensory nerves, action on, 251
 Sera, 29
 Seriparium, 332
 Sero-vaccines, 686
 Serpentina, 330
 Serum, Antidysentericum, 677
 Antilytic, 682
 Antimeningococcus, 678
 Antipneumococcus, 680
 Antistreptococcus, 682
 Antitetanic, 675
 Antitoxic, 671
 Antivenom, 678
 Convalescent, 666
 Disease, 683
 Mercurialised, 478
 Moebius's, 620
 Mode of administration, 669
 Normal, 682
 of Thyroidectomised Sheep, 620
 Salvarsanised, 501
 Sclavo's, 681
 Sickness, 683
 Thyrolitic, 620
 Sesame Oil, 650
 Serum Præparatum, 660
 Sex Glands, 431
 Shadow meal, 107
 Sherry, 142
 Shetsar, 656
 Shiga's Antidysenteric Serum, 677
 Shohaga, 572
 Sialagogues, 325
 Siberian Fir, Oil of, 523
 Sifting, 9
 Silverarsphenamin, 493
 Silver Gelatose, 123
 Nitrate, 123
 Protein, 123
 Salvarsan, 493
 Skin, action on, 642
 Skiodan, 403
 Slaked Lime, 102
 Small Chillies, 530
 Snake Venom, 625, 679
 Snow, Carbon Dioxide, 304
 Snuff, Ferrier's, 481
 Soamin, 494, 511
 Soap Bark, 317
 Castile, 657
 Curd, 657
 Ether, 657
 Green, 657
 Hard, 657
 Olive Oil, 657
 Soft, 657
 Soda, 69
 Fatarata, 343
 Sodæ Chloratæ Liquor, 551
 Tartrate Effervesens, Pulvis, 344
 Sodii Ammarsonas, 494
 Arsenas Anhydrosus, 486
 Benzoas, 438
 Bicarbonas, 69
 Biphosphas, 344
 Bromidum, 209
 Cacodylas, 494
 Carbonas, 69
 Exsiccatus, 70
 Monohydratus, 70
 Chaulmoogras, 575
 Chloridum, 81
 Citras, 76
 et Pot Tartras, 343
 Glycerophosphas, 137
 Hippuras, 438
 Hydnocarpus, 575
 Hydroxidum, 69
 Iodidum, 501
 Mandelas, 399
 Nitris, 302
 Phenolsulphonas, 559
 Phosphas, 344
 Acidus, 344
 Salicylas, 431
 Sulphas, 344
 Sulphocyanas, 87
 Thiosulphas, 86
 Sodium amytal, 207
 Antimonyl Tartrate, 505
 Aurothiomalate, 133
 Biborate, 572
 Caffeine Iodide, 385
 Dihydrogen Phosph, 344
 Dimethylarsonate, 494
 Evipan, 202, 207
 Gynocardate, 575
 Indigotindisulphonate, 403
 Iodo-methane Sulphonate, 403
 Margosate, 710
 Morrhuate, 590
 Oleate, 657
 Rhodanate, 87
 Soneryl, 207
 Stearate, 657
 Sulphocarbolate, 559
 Thiocyanate, 87
 Soft Paraffin, 659
 Soap, 657

- Solganal, 135
 Soluble Barbitone, 201
 Fluorescein, 568
 Phenobarbitone, 201
 Saccharin, 663
 Solu-septamine, 515
 Solution, 9, 23
 Donovan's, 465, 486
 Fowler's, 486
 Lock's, 81
 Lugol, 554
 Ringer's, 81
 Saturans, 572
 Vlemmckx', 582
 Volkmann's Thymol, 545
 Wright's, 84
 Somatose, 595
 Somnifaine, 202
Sondaler ata, 348
 Soneryl, 203, 207
 Sodium, 207
 Sora, 79
 Soya, 536
 Spanish flv., 647
 Sparteinæ Sulphas, 251
 Spasmodin, 438
 Spinal Anæsthesia, 258
 depressants, 214
 stimulants, 214
 Spinocain, 254
 Spirits, 30
 Spirit of Sal Volatile, 90
 of salt, 110
 Rectified, 141
 Spiritus Æthereis, 155
 Co., 155
 Nitrosi, 394
 Chloroformi, 153
 Capillaris, 562
 Glycerilis Nitratis, 300
 Juniperi, 395
 Mentholis Co., 544
 Methylatus Industrialis, 141
 Resorcinolis, 562
 Spleen, the, 621
 Spogel seeds, 709
 Sprays, 42
 Squill, 280
 Standardisation, 11
 Staphylococcal Vaccine, 690
 Staphylococcus Antitoxin, 677
 Assay of, 13
 Toxoid, 677
 Starch, 656
 Stearoptenes, 6, 540
 Steatina, Steatins, 42
 Sterilisation, 732
 Sterilised water, 383
 Stibamine. Urea, 506
 Stibenyl, 506
 Stibosan, 506
 Sticks, 42
 Stilbæstrol, 423
 Stimulant, Cerebral, 140
 Expectorant, 308
 Glycogenic, 365
 Respiratory, 304
 Spinal, 214
 Vascular, 286
 Stockholm Tar, 564
 Stock Vaccine, 665, 684
 Stomach, action on, 325
 Desiccated, 630
 Stomachics, 327
 Stovaine, 253, 261
 Stovainol, 493, 512
 Stramonium, 248
 Streptococcal Vaccine, 690
 Streptocide, 514
 Strophanthus, 277
 Assay of, 12
 Strophanthinum, 278
 Strvchnine hydrochlor, 215
 Cacodylas, 494
 Stupe, Turpentine, 41
 Styles, 42
 Stypticin, 174
 Styptics, 286
 Stypten, 679
 Strvcol, 322
 Styxax, 525
 Subchloride of Mercury, 467
 Sublimation, 9
 Sublimed Sulphur, 578
 Sublingual administration, 43
 Sucrose, 594
 Sudorifics, 643
 Suet, 660
 Sugar, Cane, 594
 Coating, 724
 of Lead, 118
 of Milk, 594
 Refined, 594
 Sulfarsenol, 492
 Sulphanilamide, 514
 Sulpharsphenamine, 492
 Sulpharsphenamine assay of, 12
 Sulphide of Barium, 108
 Sulphocarbonate of Soda, 559
 of Zinc, 127
 Sulphonol, 199
 Sulphonamide, 514
 Sulphonethylnethane, 199
 Sulphonemethane, 199
 Sulphur precipitatum, 579
 Sublimatum, 578
 Sulphurated potash, 581
 Sulphuric acid, 112
 ether, 155
 Sumatra Benzoin, 437
 Sunlight, 696
 Suppositories, 30, 729
 Suppositorium Plumbi Co., 118
 Adrenalinæ, 287

Suprarenal Cortex, 618
 Suprarenum, 287
 Suspending agents, 715
 Sweat, action on, 643
 Sweet Spirit of Nitre, 394
 Sympathetic System, action on, 223
 Synergism, 51
 Synthalam, 618
 Synthetic Ephedrine, 296
 Syrian Tragacanth, 656
 Syrups, Syrups, 31
 Syrup, Easton's, 215, 444, 630
 Partish's, 630
 Syrupus Acacie, 655
 Adhatode, 701
 Apomorphine, 315
 Calen Hypophosphitis, 136
 Lactophosphatis, 96
 Chloralis, 191
 Codeine Phosph., 188
 Corn, 595
 Ferri hypophosphitis, 633
 Glycerophosph. Co., 137
 Hypophosphitum Co., 633
 Ipecacuanhae, 310
 of liquid glucose, 721
 Pisic Liquid, 565
 Pm, 523

T

T.A.B. Vaccine, 688
 Tabella, 32
 Glyceris Trinitratis, 301
 Phenolphthalein Co., 357
 Trinitrini, 301
 Taka Diastase, 335
 Tamarindus, 348
 Tannic Acid, 367
 Tannigen, 367
 Tannin, 367
 Tannoform, 368
 Tar, 564
 Coal Prepared, 564
 Stockholm, 564
 Wood, 564
 Tartar, Cream of, 343
 Emetic, 505
 Salt of, 69
 Tartarated, Soda, 343
 Tartaric Acid, 110
 Tasteless Purgine Salt, 344
 Quinine, 445
 Teel Oil, 650
 Temperament, 50
 Terebinthum, 522
 Terminalia Arjuna, 709
 Terpine Hydras, 520
 Terpinol, 520
 Tertiary amyl alcohol, 198
 Testicles, The, 424
 Testosterone, 424

Tetanus Antitoxin, 675
 assay of, 13
 Tetra-chloretylene, 379
 Tetra-chlor phenolphthalein, 358
 Tetra ethyl of lead, 121
 Tetra-iodo-Pyrrrol, 557
 Tetronal, 199
 Teum, 702
 Thallium, 135
 Thebaine, 183
 Theelin, Thecelol, 423
 Theme, 385
 Theobromatis Oleum, 662
 Theobromina, 391
 et Sodii Acetas, 391
 Salicylas, 390
 Theobromine Cal. Salicylate, 391
 Sodium-iodo-Salicylate, 391
 Theocaine, 391
 Theocin, 392
 Sod. Acetate, 391
 Theominal, 202
 Theophylline, 390
 cum Æthylenediamine, 391
 et Sodii Acetas, 391
 Therapeutics, 1
 Accessory, 2
 Empirical, 1
 Rational, 2
 Thiocol, 322
 Thio-resorcinol, 563
 Thiosinamina, 530
 Thymol, 545
 Solution (Volckmann's), 545
 Thymolis Iodidum, 557
 Thymus, The, 620
 Thyroidectin, 620
 Thyroid Extract, 606
 Gland, 619
 Thyrolytic Serum, 620
 Thyroxinsodium, 606
 Tincturae, Tinctures, 32
 Preparations of, 730
 Tinctura Aconiti, 282
 Adhatode, 701
 Alstonite, 705
 Antiperiodica, 445
 Apocyni, 281
 Azadirachtae Indicae, 710
 Berberis, 704
 Buchu, 402
 Camphoræ, 541
 Co., 173, 541
 Cannabis, 190
 Chloroform Co., 153
 et Morphine Co., 153, 174
 Cubebæ, 703
 Ephedra, 293
 Euonymi, 363
 Gelsemi, 251
 Guaiaci ammon., 600
 Hydrastis, 415

Tinctura Iodi, 554
 Jalapæ Co., 702
 Kaladanæ 702
 Lavandulæ Co., 539
 Phosphori Co., 136
 Picrorhizæ, 705
 Warburg's, 445
 Tinnevely Senna, 355
Tist, 651
 Tocopherol, 593
 Tolerance, 49, 664
 Tolu, Balsam of, 526
 Totaquina, 443
 Toughened Caustic, 123
 Toxicology, 1
 Toxins, 34
 Toxinum Diphthericum Calefac, 672
 Detoxicat, 673
 Diagnosticum, 673
 Tragacantha, 656
 Tribromethyl alcohol, 197
 Tribromophenol, 559
 Trichloracetic acid, 109
 Trichlorphenol, 559
 Trimethylene, 167
 Trinitrophenol, 563
 Trional, 199
 Triticum, 709
 Triturations, 42
 Trochisci, Troches, 34
 Sulphuris, 579
 Tropacocaine, 253
 Trypanosomiasis, drugs used in, 511
 Triparamide, 493, 511
 Trypsin, 334
 Trypsogen, 334
 Tuberculin, P. P. D., 693
 Tuberculinum Pristinum, 691
 assay of, 13
 Turkev Rhubarb, 353
 Turkish Bath, 39
 Turpentine Oil, 520
 Stupe, 41
 Turpethum, 702
Tutia, 128
 Twilight Sleep, 247
 Typhoid, 431
 Tyndallisation, 733
 Tyramine, 409

U

Ultra-violet Rays, 696
 Unguenta, 35
 Unguentum Acidæ Chrysophanicæ, 577
 Adrenalinæ et Cocainæ, 287
 Comm, 250
 Cupræ Oleatis, 128
 Extensa, 42
 Gallæ c. Opio, 174
 Hamamelidis, 371
 Hydrarg. Iodidi Rubri, 466

Unguentum Hydrarg. Subchlor. Co., 467
 Kaolin, 132
 Methylis Salicyl. Co., 437
 Myrobalani, 707
 c. Opio, 707
 Picris Pini, 565
 Plumbi Oleatis, 119
 Sulphuris Co., 578
 Thymol, 545
 Trinitrophenolis, 563
 Unna's Paste, 20, 127, 598
 Uradal, 201
 Urari, 249
 Urea, 393
 Quinine, 393
 Stibamine, 506
 Urethane, 208
 Urinary Antiseptics, 396
 Urine, action on, 382
 Uroselectan, 403
 Urotropine, 396
 Uterine Sedatives, 424
 Uterus, action on, 404
 Uvaleral, 201

V

Vaccina, 36
 Vaccine, Antiplague, 688
 Anti-rabic, 689
 Antityphoid, 688
 paratyphoid, 688
 Autogenous, 684
 B. C. G., 693
 Curative, 689
 Detoxicated, 665, 686
 Diaplyte, 686
 Dosage of, 684
 effects of, 685
 Formolised, 686
 Lymph, 687
 Nonspecific, 684
 Ordinary, 686
 Pertussis, 690
 Pneumococcus, 690
 Prophylactic, 684
 Sensitized, 686
 Specific, 684
 Stock, 684
 T. A. B., 688
 Varieties of, 686
 Vacuum Vaccine, 687
 Typho-paratyphosis, 688
 Valerian, 532
 Valiolol, 544
 Vallet's Mass, 631
 Vapor Ammonii Chloridi, 91
 Bath, 39
 Creosoti Co., 322
 Eucalypti Co., 527
 Iodi Ætherealis, 555
 Terebinæ, 522

Varnishes, 42
 Varnishing, Pills, 725
 Vascular Stimulants, 286
 Vaso-constrictors, 287
 Vaso-dilators, 297
 Vaso-motor Centre, action on, 284
 Vaso-pressm, 415
 Vegetable, Astringents, 367
 Bitters, 328
 Calomel, 362
 Diuretics, 395
 Trocar, 281
 Venene, 679
 Venom, Cobra, 679
 Mocassin, 625, 679
 Snake, 625, 679
 Viper, 679
 Ventriculin, 630
 Ventriculus Desiccatus, 630
 Vexyl ether, 166
 Veramon, 205
 Vermicides, 372
 Vermifuges, 372
 Veronal, 200
 Sodium, 201
 Vesicants, 645
 Vessels, Drugs acting on, 284
 Viburnum, 424
 Vienna Paste, 69
 Vina, 42
 Vinegar, 109
 Vineshene, 166
 Vinum antimoniale, 505
 Viola Crystallina, 570
 Viride Malachitum, 570
 Nitens, 570
 Virol, 621
 Vitamin, 583
 Assay of, 13-14
 A, 583
 B₁, 584
 B₂, 585
 C, 587
 D, 588
 E, 593
 K, 593
 P, 594
 Vitriol, Blue, 128
 Elixir of, 113
 White, 126
 Vlemmickx' Solution, 582
 Volatile Oils, 6, 26 518
 Volckmann's Thymol Solution, 545
 Von-Hyden, 506

W

Wafer-papers, 42
 Warburg's Tincture, 445

Wash, Black, 467
 Washing Soda, 69
 Water, 15, 382
 Aromatic, 16
 Distilled, 382
 Goulard, 118
 Lime, 102
 Osmu, 706
 Sterilised, 16, 383
 Waves, 6
 Weights, 9
 in Prescription, 55
 Wet sheet-pack, 37
 Whisky, 142
 White Arsenic, 486
 Beeswax, 661
 Chinese, 127
 Corpuscles, action on, 624
 Precipitate, 467
 Soft Paraffin, 659
 Vitriol, 126
 Whitehead's Varnish, 556
 Whooping Cough Vaccine, 690
 Wild Cherry Bark, 320
 Wilkinson's Ointment, 578
 Wines, 42, 142
 Wintergreen, artificial oil of, 437
 Witch-Hazel Leaves, 371
 Wood Charcoal, 339
 Tar, 564
 Wool Fat, 15, 660
 Words, contractions of, 738
 Wright's Solution, 84
 Staphylococcal Vaccine, 690

X

Xeroform, 481

Y

Yatren, 513
 Yeast, 586
 Yellow Beeswax, 661
 Jasmine, 251
 Mercuric Oxide, 466
 Mercurous Iodide, 466
 Soft Paraffin, 659
 Yeo's mixture, 552
 Young's rule, 48

Z

Zinc paste, 127
 Preparations of, 126-127
 Sulphocarbolate, 127
 Zinc Valerianas, 533
 Zingiber, 540
 Zondek Aschheim Test, 421

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